Annex 2. Protocol

Annex 2 lists the most recent protocol amendment, Protocol Version 02, dated 15 February 2017 as well as Protocol Version 01, dated 06 July 2016.

Title Page**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
Protocol Version Identifier	P15-710 Version 02
Date of Last Version of Protocol	06.07.2016 Amendent 1: 15 February 2017
EU PAS Register Number	NA
Active Substance	NA
Medicinal Product	NA
Product Reference	NA
Procedure Number	NA
Marketing Authorization Holder(s)	EU AbbVie Ltd. Maidenhead SL6 4UB United Kingdom
Joint PASS	NA
Research Question and Objectives	This study is a non-confirmatory study to compare, in humira® (adalimumab) treated patients with axial spondyloarthritis, an active supervised and standardized training with standard of care physiotherapy in improving health-related outcomes. The primary objective is the improvement in spinal mobility after a 6 month training program. Further objectives are the improvement in physical function, health-related quality of life, disease activity, pain, psychosocial risk factors and workability.
Country(-ies) of Study	Germany
Author	

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	EU AbbVie Ltd. Maidenhead SL6 4UB United Kingdom
MAH Contact Person	NA

Protocol Amendment 1: Summary of Changes

- ***Rationale:***

Administrative change: safety reporting in section 11.1.5 changed to include non serious malignancies in patients who are 30 years of age and younger at the time of diagnosis

- The reporting of malignancies in patients who are 30 years of age or younger at the time of diagnosis was requested by the FDA for all TNF-inhibitors

1.0 Table of Contents

2.0 Abbreviations

ADA	Adalimumab
AE	Adverse Event
AMG	Arzneimittelgesetz (German Drug Law)
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
EC	Ethics Committee
eCRF	electronic case report form
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	Nonsteroidal Anti-inflammatory Drug
PAM-13	Patient Activation Measure 13
PGA	Physician's Global Assessment
PMOS	Post Marketing Observational Study
PRO	Patient reported outcome
PTGA	Patient's Global Assessment
SAE	Serious Adverse Event
QoL	Quality of life
SAP	Statistical Analysis Plan
SOC	Standard of Care
VAS	Visual analogue scale
WAI	Work Ability Index

3.0 Responsible Parties

Sponsor Main Contact	AbbVie Deutschland GmbH & Co. KG Mainzer Straße 81, 65189 Wiesbaden, Germany Phone: +49 611 1720 Fax: +49 611 1720
Principal Investigators	[redacted]
Study Designated Physician	
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Contact details and a list of investigators will be kept at AbbVie and will be available upon request.

4.0 Abstract

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
Rationale and Background: Although treated with effective medication many axSpA patients still do suffer from remarkable functional impairment and reduction in quality of life. Physical training is of fundamental importance for increasing and sustaining mobility, strength and physical fitness in general. This is also reflected in national and international guidelines, which strongly recommend physical training as the cornerstone of non-pharmacological treatment. However, there is a lack of recommendations concerning a definite type and intensity of appropriate exercise. Moreover, advice and prescription of physical training does not follow standardized procedures in Germany. In order to better understand the rational of physical training and thereby how to improve quality of health care for patients with axSpA, with this study we will analyze the impact of active supervised and standardized training in patients with axSpA.
Research Question and Objectives: This study is a non-interventional, longitudinal and non-confirmatory study to compare an active supervised training (AST) with standard of care (SOC) physiotherapy in patients with axial spondyloarthritis and stable response to Humira® (adalimumab) with respect to health-related outcomes. The primary objective is the improvement in spinal mobility after a 6 month training program. The active supervised training will be supplied by FPZ (Forschungs- und Präventions-Zentrum). SOC physiotherapy will be prescribed on physicians and performed on physiotherapist's discretion. Further objectives are the improvement in physical function, health-related quality of life, disease activity, pain, psychosocial risk factors and workability.
Study Design: Post-marketing observational study, multi-center, prospective, two-arm (Humira® + active supervised and standardized training vs. Humira® + standard of care physiotherapy), study duration 12 months from Baseline Visit.
Population: The selected study population will be adult patients (≥18 years of age) with a diagnosis of axSpA (ASAS Criteria 2009[16]) who meet the requirements per local label for treatment with Humira® (adalimumab). No prior treatment with biologic DMARDs is allowed. Patients must have initiated treatment with Humira® (adalimumab) based on current clinical practice criteria independent of the decision to participate in the study. Initiation of Humira®-treatment corresponds to the Enrollment Visit. Patients responding to Humira®-treatment based on physicians decision after 12 +/- 4 weeks and who are eligible for an active physiotherapy according to the rheumatologists and the physiotherapists estimation will be randomized to receive either an active supervised training or standard of care physiotherapy. Randomization of patients will be at Baseline Visit.

Variables:
Health-related outcomes will be assessed at the Enrollment Visit (initiation of Humira®-treatment), at Baseline Visit (after Randomization), after 3, 6, 9 and 12 month follow-up from baseline. For each follow-up time point a timeframe of ± 4 weeks will be acceptable.

Primary outcome parameter:

- Spinal mobility as measured by the Bath Ankylosing Spondylitis Metrology Index [BASMI]; 6 month after Baseline Visit, a timeframe of ± 4 weeks will be acceptable.

Secondary outcome parameters:

Time points of outcome parameter inquiry are listed in Table 1, chapter 9.1.

Improvement of spinal mobility

- Bath Ankylosing Spondylitis Metrology Index [BASMI]

Improvement of physical function

- Bath AS Functional Index [BASFI] NRS score (0 to 10)

Improvement of quality of life

- Overall functioning by ASAS Health Index (HI)

Reducing disease activity

- Disease activity as measured by Bath AS Disease Activity Index (BASDAI)
- Percentage of subjects achieving 50% improvement in BASDAI (BASDAI 50 response)
- Change from Baseline in disease activity measured by Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Percentage of subjects achieving ASDAS major improvement
- Percentage of subjects achieving ASDAS clinically important improvement
- Percentage of subjects in ASDAS inactive disease (ASDAS < 1.3)
- Percentage of subjects with low disease activity (ASDAS < 2.1)
- Percentage of subjects with moderate disease activity (ASDAS ≥1.3 to < 2.1)
- Percentage of subjects with high disease activity (ASDAS ≥ 2.1 to < 3.5)
- Percentage of subjects with very high disease activity (ASDAS ≥ 3.5)
- Percentage of subjects achieving ASAS 20
- Percentage of subjects achieving ASAS 40
- Percentage of subjects achieving ASAS Partial Remission
- Change from baseline in Physician's Global Assessment of Disease Activity
- Change from baseline in Patient's Global Assessment of Disease Activity

Improvement of pain

- Change from baseline in Patient's Global Assessment of Pain
- Change from baseline in Patient's Assessment of Total Back Pain

- Change from baseline in Patient's Assessment of Nocturnal Back Pain

Improvement of other patient-reported outcomes

- Fatigue (BASDAI question 1)
- Duration and severity of morning stiffness (mean of BASDAI questions 5 and 6)

Psychosocial risk factors

- Fear avoidance behavior (FABQ)

Other variables to be analyzed include:

- Comorbid conditions
- Concomitant medications:
  - Prior and concomitant non-biologic disease-modifying antirheumatic drugs (DMARDs)
  - Concomitant systemic glucocorticoids
  - Concomitant pain relief medications: analgesics, non-selective non-steroidal anti-rheumatic drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors

Data Sources: Real-life observational data from clinical routine assessments in patient.

Study Size: 510 axSpA patients recruited from approximately 50 rheumatologist centers

Data Analysis:

Analysis populations:

Safety set: all patients enrolled and received at least one treatment with Humira®

ITT set: all patients randomized

Per protocol set (PPS): all patients randomized and performed AST or SOC physiotherapy until 6 months without severe protocol violations

Note: Several per protocol sets might be defined according coherence with AST and SOC treatment, respectively. Those specific PPS will be defined in SAP.

Background and demographic characteristics:

Continuously scaled variables will be described by mean, standard deviation, median, min, max, Q1 and Q3. Categorical variables will be described by counts and percentages.

Analysis of primary endpoint:

The primary analysis will be performed at ITT set.

The BASMI at 6 months (V5) will be analyzed within an ANCOVA with treatment as fixed effect and baseline BASMI (V3) as covariate. The treatment effect will be reported with its 95%-confidence interval. In case prerequisites of ANCOVA are not given, according methods might be applied (transformation of data).

Note: The BASMI ($BASMI_{lin}$) is continuously scaled, because it is the mean of 5 analog measures on a scale 0 - 10.

Analysis of secondary endpoints:

Continuously scaled variables with available baseline data will be analyzed like the primary endpoint.

If baseline data are not available, 2-paired t-test will be applied.

The analysis of categorically scaled outcome variables by treatment will be performed by contingency tables. Related tests (χ^2-Test, Armitage trend test) will be performed. Binary variables will be analyzed by logistic regression.

All treatment related effects will be reported with their 95% confidence interval.

Missing data and sensitivity analyses

(1)

Missing data within questionnaires (single items are missing) will be imputed questionnaire specific rules. If such rules does not exist, missing single items will be replaced by the mean or median (details: see SAP) of the other items of the respective patient at the specific visit, if no more than 25% of the items are missing. If more than 25% of items are missing, the whole score is set to missing.

(2)

One might expect that patients finish either the AST or the SOC physiotherapy for several reasons.

In case of less than 10% of missing data for primary outcome variable, the complete case analysis is efficient. In case of more missing data, the following approaches will be applied in the sense of sensitivity analyses.

First, the underlying mechanism will be investigated by logistic regression modelling (missing information y/n = f(baseline data, success of treatment between enrollment and baseline assessment)). In case of MCAR (missing completely at random) the analysis will be performed at complete cases. In case of MAR (missing at random), multiple imputation might be applied in a sensitivity analysis. In case of MNAR (missing not at random) a specific analysis is not possible, and scenario assuming several drop-out scenario will be investigated. Such sensitivity analyses (c. g. last observation carried forward, baseline value is carried forward, missing AST will be imputed by respective SOC data) will be defined in statistical analysis plan.

Assessment of covariates

Within primary model further influencing variables (baseline data, data describing success of treatment between enrollment and baseline assessment) might be investigated. Details will be provided in SAP.

Centers could be regarded as random effects within these models (mixed models) to investigate homogeneity of the effects.

Safety data

Safety data will be described using the safety set. The data will be presented by intensity, requirement of treatment, system organ class, causality, outcome, action taken

Sample size

Assuming a treatment effect of 1 point, a standard deviation of 3.7 points and choosing 5% and 20% for type I as well as type II error, respectively, 216 patients per group are necessary. Taking into account 15% drop-out, a final study size of **510** results (216 * 2 * 1/0.85).

Data review and SAP

Data will be investigated in a blinded data review meeting in terms of protocol violations and missing data. Consequences for analysis will be taken into account in the SAP.

Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions.

Milestones: Start of Data Collection Q1 2017 End of Data Collection Q3 2019 Final Report of Study Results Q2 2020

5.0 Amendments and Updates

None

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection: Q1 2017
End of Data Collection: Q3 2019
Final Report of Study Results: Q2 2020

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions.

7.0 Rationale and Background

7.1 Background

The term axial spondyloarthritis (axSpA) covers both patients with non-radiographic axSpA (nr-axSpA) and radiographic axial SpA, the latter of which is commonly termed ankylosing spondylitis [AS]. Axial spondyloarthritis is a chronic degenerative and debilitating rheumatic disease characterized by relevant criteria such as inflammatory back pain, massive functional impairment, reduced spinal mobility and decreased quality of life.

The term "ankylosing" refers to new bone formation, which – in end stages of the disease – can lead to bridging between two vertebral bodies, whereas "spondylitis" indicates inflammation of the vertebral bodies. In its severe form, this disease results in new bone formation and finally in fusion of vertebral bodies, bony components of the sacroiliacal joint and other bones in the axial skeleton, leading to significant functional impairment and disability[1,2]. Although patients with non-radiographic axSpA have shorter disease duration and lack radiological changes, they demonstrate a substantial burden of illness, with self-reported disease activity, functional impairment and reduced quality of life comparable to patients with radiographic disease[3]. The

prevalence of axial SpA has been estimated to be between 0.2 and 1.9%, strongly dependent on the HLA-B27 prevalence in a specific country. No exact data are available on the percentage of nr-axSpA among axSpA patients but have been calculated to be around 50% in the first 10 years of the disease[4]. Due to current knowledge ca. 12% of patients with non-radiographic axial spondyloarthritis will develop radiographic lesions within two years of disease course.

7.2 Rationale

This study aims to analyze the effectiveness of active supervised training compared to standard of care physiotherapy in patients with axSpA in context of Humira® treatment.

The primary goal of treating patients with axSpA is to maximize long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalization of function and social participation[5].

Currently NSAIDs and TNF-blockers are the only effective and approved drugs for the treatment of axSpA. The latter are the treatment of choice in patients with axSpA after failure of NSAIDs. Recently secukinumab, an IL17 inhibitor, has been approved for the treatment of ankylosing spondylitis. TNF-blockers normalize acute phase reactants and reduce acute inflammation in sacroiliac joints and the spine as shown by magnetic resonance imaging (MRI)[6].

Besides affecting the joints, patients with inflammatory musculoskeletal diseases can also experience muscular weakness and muscular tissue loss which together with fatigue and anemia, other comorbidities and disease specific symptoms can negatively affect cardiovascular performance, muscle function and mobility, and thereby also reduce levels of physical activity[7]. Thus, despite treatment with effective medication many patients still suffer from remarkable functional impairment with ongoing decrease in spinal mobility over time and reduction in quality of life[8,9]. Approximately 40% of axSpA patients had considerable limitations in physical function according to the German Kerndokumentation registry from 2013 (70% or less of full function

assessed via the Hannover Functional Ability Questionnaire [FFbH])[10]. Almost half of them even had a poor functional status of less than 50% of full function. Impairment in physical function limits work ability and can even result in permanent work disability[11]. Poor function has been revealed as a major cost driver in the health-economic system as shown by an economic analysis performed by Huscher and colleagues[12] using data from the National Database of the German Collaborative Arthritis Centers. The proportion of patients receiving disability pension differed by a factor of 5 to 10 between good and poor functional status[12]. Indirect costs, due to sick leave and permanent work disability, differed by a factor of 5 between good and poor functional status which is obviously a result of the fact that only a small proportion of patients with a functional status of less than 50% of normal is able to work and those who still worked had frequent and long phases of sick leave[12]. Besides limited work capability, impairment in physical function has also a negative impact of social participation and quality of life[11,13].

In order to increase and sustain mobility, maintain physical function and muscle strength guidelines strongly recommend regular physical training as the cornerstone in the treatment of axSpA together with anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor (TNF)-inhibitors[5,14]. Additional goals of regular exercise are alleviation of pain, posture improvement and fall prevention. Supervised exercises, individually or in a group, should be preferred as these are more effective than home exercises[5,14].

However, the optimal exercise program for patients with axSpA has not been determined and it has not been put into practice for most patients[8,9]. So far there are no definite recommendations on type of exercise and intensity and it does not follow standardized procedures in Germany[9].

The recently published American College of Rheumatology recommendations for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis are more precise on which type of physical therapy should be preferred. For patients with active axSpA active physical therapy interventions (supervised exercise) are conditionally recommended over passive physical therapy interventions (massage, ultrasound, heat)[15], due to the fact that there is still limited evidence and further

research is required to analyze the impact of active supervised training in patients with axSpA.

There is sound evidence for the treatment of non-specific back pain patients that intense active supervised training is highly effective to treat back pain and to improve functional impairment.

In current and relevant literature describing different treatment regiments for axSpA patients, BASMI improvement after structured training was measured on top of a stable anti-TNF response. Liang et al. (2015) analyzed five studies to compare the effectiveness of physical activity on the disease outcome of axial SpA patients. Included in the afore mentioned meta-analysis is a study by Masiero et al. (2014) which analyzed different patient groups with an average BASMI of 4.6 to 5.2 prior to anti-TNF therapy. A BASMI improvement of 0.97 on average could be detected after 9 month of anti-TNF treatment. After subsequent randomization into three arms ("Rehabilitation Group" - intense training; "Educational Group" - education on disease awareness; "Control Group" - no intervention) a further 1.3 points improvement in BASMI could be detected in the Rehabilitation Group. Whereas in the Educational Group no difference was observed and in the Control Group a worsening of BASMI was detected. These data suggest that even a greater improvement in BASMI can be achieved under a structured training regime on top of a stable anti-TNF response compared to an anti-TNF treatment alone.

In Germany, FPZ (Research and Prevention Center) has established an active supervised training concept for back-pain patients, which will be applied and assessed in this study and compared to standard of care physiotherapy. The intensive active supervised training program consists of 24 units of exercise within 20 weeks and is focused on back fitness, core strengthening and patient engagement to treat back pain and functional impairment due to different states of muscular deconditioning. Thereby FPZ provides a standardized but highly individualized training concept, which is performed in certified training/physiotherapy centers. The training concept is described in more detail in Annex 1.

The humira® treatment of axSpA patients will be according to the local humira® product label and local standard of care, including clinical visit timing, required

laboratory tests and any other procedures required for appropriate therapy. The patients will use commercially available humira® which will be prescribed per local prescribing guidelines and local product label. Prescription of humira® will rely on therapists' decision and will be made independently to the inclusion of the patient in the PMOS. humira® therapy has a well-established and well described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since the first approved indication in 2003 for Rheumatoid Arthritis in the EU.

Participants will be instructed to contact their physician in case of an emergency, or if at any time they are in need for a consultation.

8.0 Research Question and Objectives

We hypothesize that in axSpA patients treated with humira® (adalimumab) an active supervised training is superior to standard of care physiotherapy in improving health-related outcomes.

To address this research question we will conduct a two-arm observational study with axSpA patients who, based on physicians' decision, are responding to humira® treatment and are eligible for active physiotherapy. Patients will be randomized to receive either active supervised and standardized training (AST group) or standard of care physiotherapy (SOC group).

The active supervised and standardized training consists of 24 units of exercise within 20 weeks and will be performed in certified FPZ training centers. After the 20-week training program, patients in the AST group who have still muscular deconditioning of Stage II or worse will be offered a subsequent training program consisting of 10 units within 8 to 10 weeks. The training concept is described in detail in Annex 1.

Standard of care physiotherapy as used here includes active as well as passive training and massages according to the physiotherapist discretion. The type of physiotherapy will be documented in the eCRF. Due to a lack of structured guidance in the treatment recommendations the quality and quantity of physiotherapy within the SOC arm will

not precisely be defined. Instead, the SOC arm will reflect the status quo of current physiotherapy treatment regime in Germany and thus will provide a real world comparison to generate real world evidence.

Health-related outcomes will be assessed at the Enrollment Visit (initiation of humira® treatment), at the Baseline Visit (after Randomization), after 3, 6, 9 and 12 month follow-up from baseline. For each follow-up time point a timeframe of ± 4 weeks will be acceptable.

The primary objective of this study is to compare active supervised training with standard of care physiotherapy in improving spinal mobility after 6 month from Baseline Visit in axSpA patients in context of humira® therapy.

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

Due to the non-interventional, observational character of the study, any action will be based on the physicians' decision due to analysis of axSpA patient data, which will reflect clinical routine. No additional diagnostic or monitoring procedures will be applied.

9.0 Research Methods

9.1 Study Design

Treatment of axSpA patients with humira® will be according to the local humira® product label and local standard of care, including timing of clinic visits, required laboratory tests and any other procedures required for appropriate therapy. Patients on humira® therapy have received the local patient information, and should be advised of the potential benefits and risks of humira® by their physicians as well as being instructed in injection techniques. Humira® will be obtained as commercially available medication. AbbVie will not provide the medication for this study.

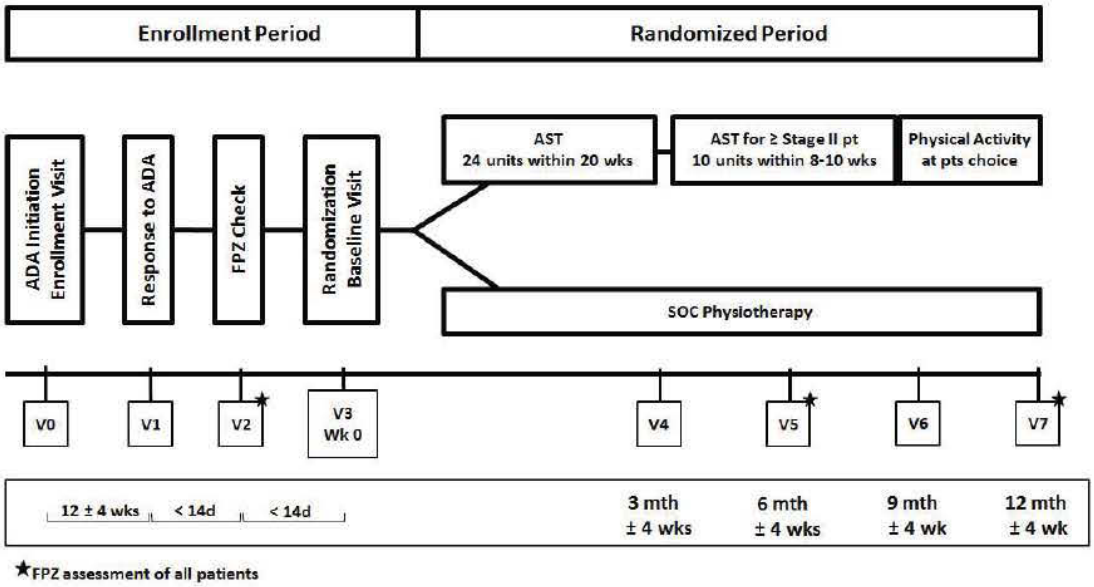
This protocol describes a post-marketing, observational study that will exploratively investigate the impact of active supervised training compared to standard of care physiotherapy in context of humira® treatment.

Adult axSpA patients initiating treatment with humira® (adalimumab) based on current clinical practice criteria will be informed about the study. After written consent they will be enrolled in the study at the Enrollment Visit. Patients with sufficient response to humira® treatment within 12 +/- 4 weeks (as defined individually by the treating physician) and who will be eligible for active physiotherapy (according to the rheumatologist's and the physiotherapist's decision) will be randomized in an 1:1 ratio to receive either active supervised training (AST group) or standard of care physiotherapy (SOC group) (Fig.1). Randomization of the patients will be balanced regarding gender, age and disease activity (BASDAI).

Patients not eligible for FPZ training will be excluded from the study. Eligibility to participate in the study is based on the basic ability of the patient to undergo active physical exercise. The decision will be based on the physicians and the physiotherapist's discretion.

The observational period of the study will comprise a follow-up period of 12 month after Baseline Visit. An enrollment period of treatment initiation and response assessment for 3 to 5 month will precede Baseline Visit and Randomization (Fig. 1).

Figure 1: Study Design Schematic



Study procedures will be performed as outlined in the schematic presented Table 1.

Table 1 and Table 2: Study Activities

Table 1: Study Activities	**Start ADA (Enrollment Visit) V0**	**Response Assessment V1**	**FPZ Assessment V2**	**Randomization (Baseline Visit) V3**	**3 Month follow-up from baseline V4**
Patient Authorization	X				
Inclusion/Exclusion Criteria	X[1]	X[2]	X[3]		
Age, gender, body weight, height, smoking	X				
Social-, educational background	X				
Non-axSpA Medical/Surgical History	X				
axSpA Medical/Surgical History	X				
Disease duration	X				
Family history	X				
HLA-B27	X				
Comorbidities	X				
Prior axSpA- medication	X				
Current axSpA- medication	X	X		X	X
Concomitant medication	X	X		X	X
Type of regular physical exercise	X				
Type of physical therapy	X	X		X	X
Serious Adverse Events /Adverse Events	X	X	X	X	X
CRP or ESR / Blood Sampling as per routine	X	X		X	X
BASMI$_{lin}$	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
Fear avoidance behavior	X	X		X	X

questionnaire (FABq)					

1. Inclusion Criteria: Patients diagnosed with axSpA, aged at least 18 years; Prescription of humira® for treating axSpA according to the local product label; Patients must have signed written informed consent before starting any study-related assessments or procedures;
   Exclusion Criteria: Patients with poorly controlled medical condition(s), which in the opinion of the investigator, would put the subject at risk by participation in the protocol; Patients with total spinal ankylosis based on the investigators' assessments of available radiographs; Any prior treatment with a biologic DMARD is prohibited
2. Inclusion Criteria: Response to humira® therapy after 12 +/- 4 weeks (no therapy escalation or change in treatment regime is required due to rheumatologist's opinion); Eligible for active physiotherapy according to the rheumatologist
3. Inclusion Criteria: Eligible for active physiotherapy according to the physiotherapist (according to FPZ requirements)

Table 2: Study Activities Follow-up	**6 Month follow-up from baseline V5**	**9 Month follow-up from baseline V6**	**12 Month follow-up from baseline V7**
Comorbidities	X	X	X
Current axSpA- medication	X	X	X
Concomitant medication	X	X	X
Type of regular physical exercise	X	X	X
Type of physiotherapy	X	X	X
Serious Adverse Events /Adverse Events	X	X	X
CRP or ESR / Blood Sampling as per routine	X	X	X
BASMIlin	X	X	X
BASFI	X	X	X
ASAS-HI	X	X	X
ASDAS	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
Fear avoidance behavior questionnaire (FABq)	X	X	X

9.2 Setting

Approximately 510 patients with axSpA (ASAS Criteria 2009[16]) who receive humira® (adalimumab) according to the local product label and who fulfill the study eligibility criteria will be enrolled. It is expected that the number of 510 patients treated with humira® is sufficient to meet the objectives of this PMOS. Approximately 50 rheumatologists will contribute to enroll eligible patients in this study.

Patients who consent to participate in the study will be observed for up to 12 month from baseline. Physicians should treat enrolled axSpA patients just as they treat axSpA patients in the routine clinical practice. Patients may discontinue humira® treatment or the study at any time for any reason. Following discontinuation of humira®, the patient will be treated in accordance with the investigator's best clinical judgment.

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

○ SAE: reported to AbbVie within 24 hours of physician awareness

○ Non serious AE: reported to AbbVie within 24 hours of physician awareness

Patients that end humira® treatment or start treatment on any other biologic marketed in the EU will be withdrawn from the study and will not be part of the primary analysis population.

If a patient withdraws or is lost to follow-up, every effort should be made to note such along with the reason for withdrawal in the electronic case report form (eCRF).

Inclusion Criteria

A patient will be eligible for study participation if he/she meets the following criteria:

- Patients diagnosed with axSpA (either AS or nr-axSpA), fulfilling the ASAS classification, aged at least 18 years
- Prescription of humira® for treating axSpA according to the local product label

- Eligibility for active physiotherapy according to the rheumatologist and physiotherapist
- Patients must have signed written informed consent before starting any study-related assessments or procedures

Exclusion Criteria

A patient will not be eligible for study participation if he/she meets any of the following criteria:

- Patients with total spinal ankylosis based on the investigators' assessments of available radiographs
- Patients who are not eligible for active supervised training or active physiotherapy at the discretion of the rheumatologist and/or the physiotherapist
- Patients with poorly controlled medical condition(s), which in the opinion of the investigator, would put the subject at risk by participation in the protocol
- Any prior treatment with a biologic DMARD is prohibited

9.3 Variables

Health-related outcomes will be assessed at the Enrollment Visit (initiation of humira® treatment), at the Baseline Visit (after Randomization), after 3, 6, 9 and 12 month follow-up from baseline. For each follow-up time point a timeframe of ± 4 weeks will be acceptable.

The primary outcome parameter is the improvement of spinal mobility after 6 month from Baseline Visit as measured by the Bath Ankylosing Spondylitis Metrology Index [BASMI] in the AST group as compared to SOC group.

BASMI is an objective measure to capture in detail the range of movement and spinal mobility. Its sensitivity is proven for the measurements of spinal mobility impairment during the stages of the axSpA disease course. Further, BASMI will provide an

objective readout as it does not depend on PRO parameters and thus will be less confounded by psychosocial factors.

Importantly, relevant exercises of the established training concept developed by the AST provider directly correlate with four of the five BASMI measures. Hence, BASMI will be the optimal, objective and validated measure of choice to observe spinal mobility of the AST population vs the SOC population.

PROs were not chosen as primary outcome parameter as psychosocial factors render them less objective. Research has shown that patients with a high risk of depression and anxiety score higher in BASDAI, BASFI, EQ5D and ASDAS-CRP as well as in the overall pain score (VAS) and ASQoL. Nevertheless, besides somatic parameters, the accurate assessment of psychosocial risk factors, by the above mentioned appropriate questionnaires is of high importance. Therefore, the selected measures will be used.

Secondary outcome parameter will include the following:

- Spinal mobility – Evaluated by the Bath Ankylosing Spondylitis Metrology Index [BASMI]
- Physical Function – Evaluated by the BASFI NRS score (0 to 10)
- Overall functioning by ASAS Health Index (HI)
- Disease activity as measured by Bath AS Disease Activity Index (BASDAI)
- Percentage of patients achieving 50% improvement in BASDAI (BASDAI 50 response)
- Disease activity as measured by Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Percentage of patients in ASDAS inactive disease (ASDAS < 1.3)
- Percentage of patients with low disease activity (ASDAS < 2.1)
- Percentage of subjects with moderate disease activity (ASDAS ≥ 1.3 to < 2.1)
- Percentage of subjects with high disease activity (ASDAS ≥ 2.1 to < 3.5)
- Percentage of subjects with very high disease activity (ASDAS ≥ 3.5)
- ASDAS major improvement ($\Delta \geq 2.0$)
- ASDAS clinically important improvement ($\Delta \geq 1.0$)

- ASAS 20, ASAS 40, and ASAS Partial Remission
    - ASAS20 response: improvement of ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit)
        - Patient's Global Assessment – Represented by the PTGA-disease activity NRS score (0 to 10)
        - Pain – Represented by the patient's assessment of total back pain NRS score (0 to 10)
        - Function – Represented by the BASFI NRS score (0 to 10)
        - Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10])
    - ASAS40 response: improvement of ≥ 40% and absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in ≥ 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain Function as measured by Bath AS Functional Index (BASFI NRS)
    - ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20
- Patient's Global Assessment of Pain
- Patient's Assessment of Total Back Pain
- Patient's Assessment of Nocturnal Back Pain
- Work Ability Index (modified WAI)
- Fatigue (BASDAI question 1)
- Duration and severity of morning stiffness (mean of BASDAI questions 5 and 6)

Psychosocial risk factors

- Fear avoidance behavior (FABQ)

Other variables evaluated include:

- Comorbid conditions
- Concomitant medications:
    - Prior and concomitant non-biologic disease-modifying antirheumatic drugs (DMARDs)

- Concomitant systemic glucocorticoids
- Concomitant pain relief medications: analgesics, non-selective non-steroidal anti-rheumatic drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors

9.4 Data Sources

The reported data for the study will be available from the patient's file as well as the documentation done at the FPZ training center.

9.5 Study Size

Ciprian et al. (2013), Masiero et al. (2014) and Ygrit et al. (2013) show BASMI improvement of one point in populations receiving structured physiotherapy, compared to control groups (Liang et al. 2015). With the assumed detectable difference of one BASMI point, an assumed power of 80% and a standard deviation of 3.7 the sample size per arm is calculated to be 216 patients (total 432 patients).

Due to a complex enrolment flow, the long duration of the non-interventional study and the physical exposure of the patients we may expect a dropout rate of 15%, resulting in a total enrolment of 510 patients.

9.6 Data Management

Data for this study will be recorded in German by each participating center via an electronic data capture (EDC) system using a web-based eCRF with a unique subject ID code on a web-based encrypted platform. The participating site enters all data following pseudonymization. Data of clinical examination, diagnostic measures, laboratory assessments, findings and observations routinely performed in patients with humira® therapy included in this cohort, will be transcribed by hand by the rheumatologist or study nurse from the source documents into the eCRF. And the source documents will be stored on site. Only data specified in the protocol will be

entered into the eCRF. For each enrolled patient, the investigator or designee will create a new patient file in the eCRF and a unique patient number will be automatically allocated by the system. A comprehensive data validation program utilizing front-end checks in the eCRF will validate the data. Plausibility checks on defined limits and variable values will take place automatically. Automated checks for data consistency will be implemented; discrepancies need to be solved by the researcher in the eCRF before the module can be completed.

Follow-up on eCRF data for medical plausibility will be done by AbbVie medical personnel (or their representatives). Queries will be generated in the eCRF for online resolution at the site. The investigator or an authorized member of the investigator's staff will make any necessary data corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. The principal investigator will finally review the eCRFs for completeness and accuracy of available data and provide his or her electronic signature and date to the eCRFs as evidence thereof. In addition, a qualified representative of the AbbVie medical department who is obliged to maintain confidentiality will visit the site periodically to conduct quality assurance measures. This includes training staff before study initiation, answering questions and clarifying any queries. Source data verification may be organized in collaboration with study personnel.

Access to the EDC system will be provided for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (e.g. CD-ROM) and provided to the investigator as a durable record of the site's eCRF data. Original Questionnaires will be sent from the participating site to:

e.factum GmbH
Werner-von-Siemens-Straße 1
35510 Butzbach


[redacted]

9.7 Data Analysis

9.7.1 Analysis populations:

Safety set: all patients enrolled and received at least one treatment with Humira®

ITT set: all patients randomized

Per protocol set (PPS): all patients randomized and performed AST or SOC physiotherapy until 6 months without severe protocol violations

Note: Several per protocol sets might be defined according coherence with AST and SOC treatment, respectively. Those specific PPS will be defined in SAP.

9.7.2 Background and demographic characteristics:

Continuously scaled variables will be described by mean, standard deviation, median, min, max, Q1 and Q3. Categorical variables will be described by counts and percentages.

9.7.3 Analysis of primary endpoint:

The primary analysis will performed at ITT set.

The BASMI at 6 months (V5) will be analysed within an ANCOVA with treatment as fixed effect and baseline BASMI (V3) as covariate. The treatment effect will be reported with its 95%-confidence interval. In case prerequisites of ANCOVA are not given, according methods might be applied (transformation of data).

Note: The BASMI (BASMIlin) is continuously scaled, because it is the mean of 5 analog measures on a scale 0 - 10.

9.7.4 Analysis of secondary endpoints:

Continuously scaled variables with available baseline data will be analysed like the primary endpoint.

If baseline data are not available, 2-paired t-test will be applied.

The analysis of categorically scaled outcome variables by treatment will be performed by contingency tables. Related tests (□2-Test, Armitage trend test) will be performed. Binary variables will be analysed by logistic regression.

All treatment related effects will be reported with their 95% confidence interval.

9.7.5 Missing data and sensitivity analyses

(1)

Missing data within questionnaires (single items are missing) will be imputed questionnaire specific rules. If such rules does not exist, missing single items will be replaced by the mean or median (details: see SAP) of the other items of the respective patient at the specific visit, if no more than 25% of the items are missing. If more than 25% of items are missing, the whole score is set to missing.

(2)

One might expect that patients finish either the AST or the SOC physiotherapy for several reasons.

In case of less than 10% of missing data for primary outcome variable, the complete case analysis is efficient. In case of more missing data, the following approaches will be applied in the sense of sensitivity analyses.

First, the underlying mechanism will be investigated by logistic regression modelling (missing information y/n = f(baseline data, success of treatment between enrollment and baseline assessment)). In case of MCAR (missing completely at random) the analysis will be performed at complete cases. In case of MAR (missing at random), multiple imputation might be applied in a sensitivity analysis. In case of MNAR

(missing not at random) a specific analysis is not possible, and scenario assuming several drop-out scenario will be investigated. Such sensitivity analyses (e. g. last observation carried forward, baseline value is carried forward, missing AST will be imputed by respective SOC data) will be defined in statistical analysis plan.

9.7.6 Assessment of covariates

Within primary model further influencing variables (baseline data, data describing success of treatment between enrollment and baseline assessment) might be investigated. Details will be provided in SAP.

Centers could be regarded as random effects within these models (mixed models) to investigate homogeneity of the effects.

9.7.7 Safety data

Safety data will be described using the safety set. The data will be presented by severity, intensity, requirement of treatment, system organ class, causality, outcome, action taken.

9.7.8 Data review and SAP

Data will be investigated in a blinded data review meeting in terms of protocol violations and missing data. Consequences for analysis will be taken into account in the SAP.

Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions.

9.8 Quality Control

Prior to any study-related data being collected, patient authorization to use and/or disclose personal and/or health data will be obtained and will be reviewed and signed and dated by the patient and physician who administered the patient authorization. A copy of the signed patient authorization will be given to the patient and the original will be placed in the patient's medical record. A patient authorization for use/disclosure of data template will be provided.

Prior to the initiation of the study, rheumatologists and site personnel will be trained on the study and the FPZ concept (described in Annex 1). Training will include a detailed discussion of the protocol and study procedures (study design, patient flow, in- and exclusion criteria), patient reported outcomes (PRO) and procedure of data management (e.g. eCRF completion). FPZ personnel will be trained on medical background of axial spondyloarthritis, disease characteristics and peculiar features of patients' clinical condition in regards to physical exercise.

All data generated by the rheumatologist will be entered via the eCRF. All data generated by FPZ will be transferred to CRO and inserted into the respective patient eCRF. After entry of the data, computer logic checks will be run to check for inconsistent data.

9.9 Limitations of the Research Methods

9.10 Other Aspects

10.0 Protection of Human Subjects

This PMOS will be run in compliance with local laws and regulations (§4 German Drug Law, AMG). Notification/submission to the responsible regulatory authorities, Ethics Committee (EC), Health Insurance bodies and Competent Authorities (CAs) will be done as required by local laws and regulations.

The investigator is responsible to ensure that written informed consent to use and/or disclose patients' pseudomized health data will be obtained prior to patient inclusion.

To maintain patient confidentiality, no demographic data that can identify the patient will be collected (e.g. initials, date of birth) - only the patient age will be collected. In order to protect patient identity, a unique number will be assigned to each patient and related study recording.

11.0 Management and Reporting of Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 11.2.2). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 11.2.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

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

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

11.1.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event.

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

11.1.4 Serious Adverse Event Collection Period

Serious adverse and non-serious events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

11.1.5 Serious Adverse Event Reporting

Product-related events including Adverse Reaction Reporting

This is an observational research study not designed to identify or quantify a safety hazard relating to humira®.

If a patient reports a product-related event (e.g. suspected adverse reaction or product complaint) to his/her healthcare professional during the data collection period or the healthcare professional identifies a product-related event, which is considered related to humira® or any other AbbVie authorized product, the event should be reported to AbbVie. Any product-related events considered to be related to a non-AbbVie product should be reported in accordance with local laws and regulations to the relevant Regulatory Authority and/or drug marketing authorisation holder.

Patient Reported Outcome (PRO) data are not considered a potential source of adverse reactions. However, participating sites should review the PRO data and if a possible product-related event (including a suspected adverse reaction) is noted, the HCP must determine whether the event is related to humira® and if so, it should be reported to AbbVie.

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the physician will:

- For events from patients using and AbbVie product - notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the event.
- For events from patients using a comparator product - notify the Marketing Application Holder (MAH) for the comparator product within 24 hours of the physician becoming aware of the event.

This protocol requires all SAEs and non-serious adverse events as outlined in protocol section 11.1.1 to be actively solicited.

The relevant AbbVie Pharmacovigilance contact details are specified below:

AbbVie Deutschland GmbH & Co. KG
Arzneimittelsicherheit (AMS) AbbVie Deutschland
Mainzer Straße 81
65189 Wiesbaden, Germany
[redacted]

11.1.6 Pregnancy Reporting

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 0 within 24 hours of the physician becoming aware of the pregnancy.

11.2 Product Complaint

11.2.1 Definition

A Product Complaint is any Complaint related to the biologic or drug component of the product or to the device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

11.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product and/or device should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

The relevant AbbVie Pharmacovigilance contact details see section 11.1.5.

12.0 Plans for Disseminating and Communicating Study Results

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions. The completed eCRFs and the study report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this

study may be published by AbbVie or by any one of the participating physicians after written agreement with AbbVie.

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14.0 Annex 1. Additional Information

14.1.1 The AST provider: FPZ therapy

The FPZ therapy is an evidence-based back pain therapy based on intensive, active and supervised training which focuses on back fitness, core strengthening and patient engagement.

The FPZ concept strictly follows principal physiological and innovative knowledge for training which is reflected by the historical term FPZ (Forschungs- und Präventionszentrum, engl. Research and Prevention Center) going back to the time when the concept has been developed.

According to the individual deconditioning status the patient will perform 10 or 24 sessions within three to four months. The training is offered in "certified" FPZ-training- or physiotherapy centers and will be conducted as machine based training with a defined sequence of exercises under accurate supervision of especially trained physiotherapists or exercise physiologists. The training machines are part of an especially developed and certified high-tech equipment which is based on standardized methodology and makes possible an exact monitoring and documentation of all exercises and other relevant patient parameters.

Therapists, being especially trained and continuously educated on the FPZ-concept, assess the patient and exactly monitor the performance of all exercises. Moreover they assess and positively influence psychosocial risk factors by offering an intense assistance and support for the patients.

By definition the FPZ therapy is an interdisciplinary evidence-based medical training concept for the treatment of back pain patients with

- functional backpain
- clear medical indication and
- advanced chronification of disease pattern (stadium I or II after Gerbershagen/Schmitt) and

- advanced deconditioning of the spine stabilizing musculature (stadium 3 or 4 after Denner).

From a medical perspective, the FPZ therapy represents an integrated functional back pain therapy with the primary aim to recondition the patient. Being based on the bio-psycho-social model for back pain the FPZ therapy can firstly be applied in a predominantly curative way and subsequently in a secondary preventive way in order to stabilize the achieved success in the long run.

With help of the FPZ 4-level-diagnostics, consisting of
1. orthopedic diagnostics
2. structural diagnostics,
3. pain diagnostics and
4. functional diagnostics

it is ensured that only suitable patients enter the therapy
(= qualified suitability check and selection of back pain patients on the basis of medical necessity).
As could be demonstrated so far, the FPZ-concept on average cares for the achievement of the following parameters:

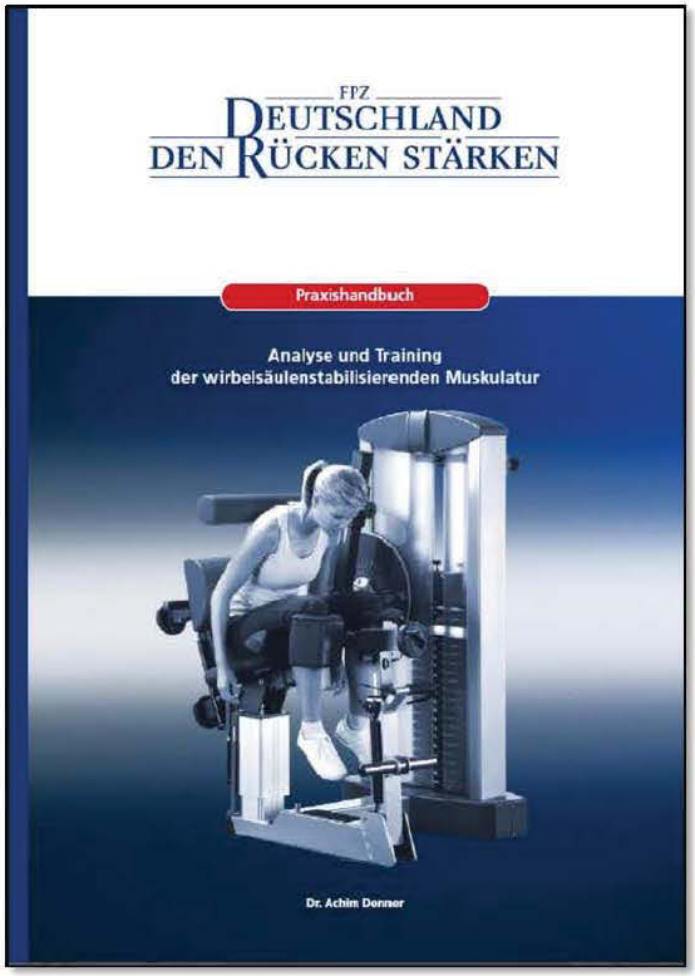
- Increase of maximum strength: +31%
- Increase of muscular performance: +67%
- Recovery of muscular dysbalances and asymmetries in >90% of cases within 6 months
- Pain reduction in > 70% of patients measured on a 0-10 NRS

Since its entrance into the health care market, the FPZ demonstrates high level effectiveness and a reliable safety profile for the treatment of back pain patients. Currently, the FPZ-concept represents the only working example for integrated health

care in Germany and thus the concept can be prescribed by experienced physicians and is reimbursed by many sick-funds.

14.1.2 The FPZ therapy handbook (German)

Separate PDF document



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
Protocol Version Identifier	P15-710 Version 01
Date of Last Version of Protocol	06.07.2016
EU PAS Register Number	NA
Active Substance	NA
Medicinal Product	NA
Product Reference	NA
Procedure Number	NA
Marketing Authorization Holder(s)	EU AbbVie Ltd. Maidenhead SL6 4UB United Kingdom
Joint PASS	NA
Research Question and Objectives	This study is a non-confirmatory study to compare, in adalimumab treated patients with axial spondyloarthritis, an active supervised and standardized training with standard of care physiotherapy in improving health-related outcomes. The primary objective is the improvement in spinal mobility after a 6 month training program. Further objectives are the improvement in physical function, health-related quality of life, disease activity, pain, psychosocial risk factors and workability.
Country(-ies) of Study	Germany
Author	

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	EU AbbVie Ltd. Maidenhead SL6 4UB United Kingdom
MAH Contact Person	NA

1.0 Table of Contents

2.0 Abbreviations

ADA	Adalimumab
AE	Adverse Event
AMG	Arzneimittelgesetz (German Drug Law)
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
EC	Ethics Committee
eCRF	electronic case report form
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	Nonsteroidal Anti-inflammatory Drug
PAM-13	Patient Activation Measure 13
PGA	Physician's Global Assessment
PMOS	Post Marketing Observational Study
PRO	Patient reported outcome
PTGA	Patient's Global Assessment
SAE	Serious Adverse Event
QoL	Quality of life
SAP	Statistical Analysis Plan
SOC	Standard of Care
VAS	Visual analogue scale
WAI	Work Ability Index

3.0 Responsible Parties

Sponsor Main Contact	AbbVie Deutschland GmbH & Co. KG Mainzer Straße 81, 65189 Wiesbaden, Germany Phone: +49 611 1720 Fax: +49 611 1720
Principal Investigators	[redacted]
Study Designated Physician	
Data Management and Statistics	
Laboratory	

Contact details and a list of investigators will be kept at AbbVie and will be available upon request.

4.0 Abstract

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
Rationale and Background: Although treated with effective medication many axSpA patients still do suffer from remarkable functional impairment and reduction in quality of life. Physical training is of fundamental importance for increasing and sustaining mobility, strength and physical fitness in general. This is also reflected in national and international guidelines, which strongly recommend physical training as the cornerstone of non-pharmacological treatment. However, there is a lack of recommendations concerning a definite type and intensity of appropriate exercise. Moreover, advice and prescription of physical training does not follow standardized procedures in Germany. In order to better understand the rational of physical training and thereby how to improve quality of health care for patients with axSpA, with this study we will analyze the impact of active supervised and standardized training in patients with axSpA.
Research Question and Objectives: This study is a non-interventional, longitudinal and non-confirmatory study to compare an active supervised training (AST) with standard of care (SOC) physiotherapy in patients with axial spondyloarthritis and stable response to adalimumab with respect to health-related outcomes. The primary objective is the improvement in spinal mobility after a 6 month training program. The active supervised training will be supplied by FPZ (Forschungs- und Präventions-Zentrum). SOC physiotherapy will be prescribed on physicians and performed on physiotherapist's discretion. Further objectives are the improvement in physical function, health-related quality of life, disease activity, pain, psychosocial risk factors and workability.
Study Design: Post-marketing observational study, multi-center, prospective, two-arm (adalimumab + active supervised and standardized training vs. adalimumab + standard of care physiotherapy), study duration 12 months from Baseline Visit.
Population: The selected study population will be adult patients (≥18 years of age) with a diagnosis of axSpA (ASAS Criteria 2009[16]) who meet the requirements per local label for treatment with adalimumab. No prior treatment with biologic DMARDs is allowed. Patients must have initiated treatment with adalimumab based on current clinical practice criteria independent of the decision to participate in the study. Initiation of adalimumab treatment corresponds to the Enrollment Visit. Patients responding to adalimumab treatment based on physicians decision after 12 +/- 4 weeks and who are eligible for an active physiotherapy according to the rheumatologists and the physiotherapists estimation will be randomized to receive either an active supervised training or standard of care physiotherapy. Randomization of patients will be at Baseline Visit.

Variables:
Health-related outcomes will be assessed at the Enrollment Visit (initiation of adalimumab treatment), at Baseline Visit (after Randomization), after 3, 6, 9 and 12 month follow-up from baseline. For each follow-up time point a timeframe of ± 4 weeks will be acceptable.

Primary outcome parameter:

- Spinal mobility as measured by the Bath Ankylosing Spondylitis Metrology Index [BASMI]; 6 month after Baseline Visit, a timeframe of ± 4 weeks will be acceptable.

Secondary outcome parameters:

Time points of outcome parameter inquiry are listed in Table 1, chapter 9.1.

Improvement of spinal mobility

- Bath Ankylosing Spondylitis Metrology Index [BASMI]

Improvement of physical function

- Bath AS Functional Index [BASFI] NRS score (0 to 10)

Improvement of quality of life

- Overall functioning by ASAS Health Index (HI)

Reducing disease activity

- Disease activity as measured by Bath AS Disease Activity Index (BASDAI)
- Percentage of subjects achieving 50% improvement in BASDAI (BASDAI 50 response)
- Change from Baseline in disease activity measured by Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Percentage of subjects achieving ASDAS major improvement
- Percentage of subjects achieving ASDAS clinically important improvement
- Percentage of subjects in ASDAS inactive disease (ASDAS < 1.3)
- Percentage of subjects with low disease activity (ASDAS < 2.1)
- Percentage of subjects with moderate disease activity (ASDAS ≥1.3 to < 2.1)
- Percentage of subjects with high disease activity (ASDAS ≥ 2.1 to < 3.5)
- Percentage of subjects with very high disease activity (ASDAS ≥ 3.5)
- Percentage of subjects achieving ASAS 20
- Percentage of subjects achieving ASAS 40
- Percentage of subjects achieving ASAS Partial Remission
- Change from baseline in Physician's Global Assessment of Disease Activity
- Change from baseline in Patient's Global Assessment of Disease Activity

Improvement of pain

- Change from baseline in Patient's Global Assessment of Pain
- Change from baseline in Patient's Assessment of Total Back Pain

- Change from baseline in Patient's Assessment of Nocturnal Back Pain

Improvement of other patient-reported outcomes

- Fatigue (BASDAI question 1)
- Duration and severity of morning stiffness (mean of BASDAI questions 5 and 6)

Psychosocial risk factors

- Fear avoidance behavior (FABQ)

Other variables to be analyzed include:

- Comorbid conditions
- Concomitant medications:
  - Prior and concomitant non-biologic disease-modifying antirheumatic drugs (DMARDs)
  - Concomitant systemic glucocorticoids
  - Concomitant pain relief medications: analgesics, non-selective non-steroidal anti-rheumatic drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors

Data Sources: Real-life observational data from clinical routine assessments in patient.

Study Size: 510 axSpA patients recruited from approximately 50 rheumatologist centers

Data Analysis:

Analysis populations:

Safety set: all patients enrolled and received at least one treatment with Adalimumab

ITT set: all patients randomized

Per protocol set (PPS): all patients randomized and performed AST or SOC physiotherapy until 6 months without severe protocol violations

Note: Several per protocol sets might be defined according coherence with AST and SOC treatment, respectively. Those specific PPS will be defined in SAP.

Background and demographic characteristics:

Continuously scaled variables will be described by mean, standard deviation, median, min, max, Q1 and Q3. Categorical variables will be described by counts and percentages.

Analysis of primary endpoint:

The primary analysis will be performed at ITT set.

The BASMI at 6 months (V5) will be analyzed within an ANCOVA with treatment as fixed effect and baseline BASMI (V3) as covariate. The treatment effect will be reported with its 95%-confidence interval. In case prerequisites of ANCOVA are not given, according methods might be applied (transformation of data).

Note: The BASMI ($BASMI_{lin}$) is continuously scaled, because it is the mean of 5 analog measures on a scale 0 - 10.

Analysis of secondary endpoints:

Continuously scaled variables with available baseline data will be analyzed like the primary endpoint.

If baseline data are not available, 2-paired t-test will be applied.

The analysis of categorically scaled outcome variables by treatment will be performed by contingency tables. Related tests (χ^2-Test, Armitage trend test) will be performed. Binary variables will be analyzed by logistic regression.

All treatment related effects will be reported with their 95% confidence interval.

Missing data and sensitivity analyses

(1)

Missing data within questionnaires (single items are missing) will be imputed questionnaire specific rules. If such rules does not exist, missing single items will be replaced by the mean or median (details: see SAP) of the other items of the respective patient at the specific visit, if no more than 25% of the items are missing. If more than 25% of items are missing, the whole score is set to missing.

(2)

One might expect that patients finish either the AST or the SOC physiotherapy for several reasons.

In case of less than 10% of missing data for primary outcome variable, the complete case analysis is efficient. In case of more missing data, the following approaches will be applied in the sense of sensitivity analyses.

First, the underlying mechanism will be investigated by logistic regression modelling (missing information y/n = f(baseline data, success of treatment between enrollment and baseline assessment)). In case of MCAR (missing completely at random) the analysis will be performed at complete cases. In case of MAR (missing at random), multiple imputation might be applied in a sensitivity analysis. In case of MNAR (missing not at random) a specific analysis is not possible, and scenario assuming several drop-out scenario will be investigated. Such sensitivity analyses (e. g. last observation carried forward, baseline value is carried forward, missing AST will be imputed by respective SOC data) will be defined in statistical analysis plan.

Assessment of covariates

Within primary model further influencing variables (baseline data, data describing success of treatment between enrollment and baseline assessment) might be investigated. Details will be provided in SAP.

Centers could be regarded as random effects within these models (mixed models) to investigate homogeneity of the effects.

Safety data

Safety data will be described using the safety set. The data will be presented by intensity, requirement of treatment, system organ class, causality, outcome, action taken

Sample size

Assuming a treatment effect of 1 point, a standard deviation of 3.7 points and choosing 5% and 20% for type I as well as type II error, respectively, 216 patients per group are necessary. Taking into account 15% drop-out, a final study size of **510** results (216 * 2 * 1/0.85).

Data review and SAP

Data will be investigated in a blinded data review meeting in terms of protocol violations and missing data. Consequences for analysis will be taken into account in the SAP.

Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions.

Milestones: Start of Data Collection Q1 2017 End of Data Collection Q3 2019 Final Report of Study Results Q2 2020

5.0 Amendments and Updates

None

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection: Q1 2017
End of Data Collection: Q3 2019
Final Report of Study Results: Q2 2020

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions.

7.0 Rationale and Background

7.1 Background

The term axial spondyloarthritis (axSpA) covers both patients with non-radiographic axSpA (nr-axSpA) and radiographic axial SpA, the latter of which is commonly termed ankylosing spondylitis [AS]. Axial spondyloarthritis is a chronic degenerative and debilitating rheumatic disease characterized by relevant criteria such as inflammatory back pain, massive functional impairment, reduced spinal mobility and decreased quality of life.

The term "ankylosing" refers to new bone formation, which – in end stages of the disease – can lead to bridging between two vertebral bodies, whereas "spondylitis" indicates inflammation of the vertebral bodies. In its severe form, this disease results in new bone formation and finally in fusion of vertebral bodies, bony components of the sacroiliacal joint and other bones in the axial skeleton, leading to significant functional impairment and disability[1,2]. Although patients with non-radiographic axSpA have shorter disease duration and lack radiological changes, they demonstrate a substantial burden of illness, with self-reported disease activity, functional impairment and reduced quality of life comparable to patients with radiographic disease[3]. The

prevalence of axial SpA has been estimated to be between 0.2 and 1.9%, strongly dependent on the HLA-B27 prevalence in a specific country. No exact data are available on the percentage of nr-axSpA among axSpA patients but have been calculated to be around 50% in the first 10 years of the disease[4]. Due to current knowledge ca. 12% of patients with non-radiographic axial spondyloarthritis will develop radiographic lesions within two years of disease course.

7.2 Rationale

This study aims to analyze the effectiveness of active supervised training compared to standard of care physiotherapy in patients with axSpA in context of adalimumab treatment.

The primary goal of treating patients with axSpA is to maximize long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalization of function and social participation[5].

Currently NSAIDs and TNF-blockers are the only effective and approved drugs for the treatment of axSpA. The latter are the treatment of choice in patients with axSpA after failure of NSAIDs. Recently secukinumab, an IL17 inhibitor, has been approved for the treatment of ankylosing spondylitis. TNF-blockers normalize acute phase reactants and reduce acute inflammation in sacroiliac joints and the spine as shown by magnetic resonance imaging (MRI)[6].

Besides affecting the joints, patients with inflammatory musculoskeletal diseases can also experience muscular weakness and muscular tissue loss which together with fatigue and anemia, other comorbidities and disease specific symptoms can negatively affect cardiovascular performance, muscle function and mobility, and thereby also reduce levels of physical activity[7]. Thus, despite treatment with effective medication many patients still suffer from remarkable functional impairment with ongoing decrease in spinal mobility over time and reduction in quality of life[8,9]. Approximately 40% of axSpA patients had considerable limitations in physical function according to the German Kerndokumentation registry from 2013 (70% or less of full function

assessed via the Hannover Functional Ability Questionnaire [FFbH])[10]. Almost half of them even had a poor functional status of less than 50% of full function. Impairment in physical function limits work ability and can even result in permanent work disability[11]. Poor function has been revealed as a major cost driver in the health-economic system as shown by an economic analysis performed by Huscher and colleagues[12] using data from the National Database of the German Collaborative Arthritis Centers. The proportion of patients receiving disability pension differed by a factor of 5 to 10 between good and poor functional status[12]. Indirect costs, due to sick leave and permanent work disability, differed by a factor of 5 between good and poor functional status which is obviously a result of the fact that only a small proportion of patients with a functional status of less than 50% of normal is able to work and those who still worked had frequent and long phases of sick leave[12]. Besides limited work capability, impairment in physical function has also a negative impact of social participation and quality of life[11,13].

In order to increase and sustain mobility, maintain physical function and muscle strength guidelines strongly recommend regular physical training as the cornerstone in the treatment of axSpA together with anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor (TNF)-inhibitors[5,14]. Additional goals of regular exercise are alleviation of pain, posture improvement and fall prevention. Supervised exercises, individually or in a group, should be preferred as these are more effective than home exercises[5,14].

However, the optimal exercise program for patients with axSpA has not been determined and it has not been put into practice for most patients[8,9]. So far there are no definite recommendations on type of exercise and intensity and it does not follow standardized procedures in Germany[9].

The recently published American College of Rheumatology recommendations for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis are more precise on which type of physical therapy should be preferred. For patients with active axSpA active physical therapy interventions (supervised exercise) are conditionally recommended over passive physical therapy interventions (massage, ultrasound, heat)[15], due to the fact that there is still limited evidence and further

research is required to analyze the impact of active supervised training in patients with axSpA.

There is sound evidence for the treatment of non-specific back pain patients that intense active supervised training is highly effective to treat back pain and to improve functional impairment.

In current and relevant literature describing different treatment regiments for axSpA patients, BASMI improvement after structured training was measured on top of a stable anti-TNF response. Liang et al. (2015) analyzed five studies to compare the effectiveness of physical activity on the disease outcome of axial SpA patients. Included in the afore mentioned meta-analysis is a study by Masiero et al. (2014) which analyzed different patient groups with an average BASMI of 4.6 to 5.2 prior to anti-TNF therapy. A BASMI improvement of 0.97 on average could be detected after 9 month of anti-TNF treatment. After subsequent randomization into three arms ("Rehabilitation Group" - intense training; "Educational Group" - education on disease awareness; "Control Group" - no intervention) a further 1.3 points improvement in BASMI could be detected in the Rehabilitation Group. Whereas in the Educational Group no difference was observed and in the Control Group a worsening of BASMI was detected. These data suggest that even a greater improvement in BASMI can be achieved under a structured training regime on top of a stable anti-TNF response compared to an anti-TNF treatment alone.

In Germany, FPZ (Research and Prevention Center) has established an active supervised training concept for back-pain patients, which will be applied and assessed in this study and compared to standard of care physiotherapy. The intensive active supervised training program consists of 24 units of exercise within 20 weeks and is focused on back fitness, core strengthening and patient engagement to treat back pain and functional impairment due to different states of muscular deconditioning. Thereby FPZ provides a standardized but highly individualized training concept, which is performed in certified training/physiotherapy centers. The training concept is described in more detail in Annex 1.

The adalimumab treatment of axSpA patients will be according to the local adalimumab product label and local standard of care, including clinical visit timing,

required laboratory tests and any other procedures required for appropriate therapy. The patients will use commercially available adalimumab which will be prescribed per local prescribing guidelines and local product label. Prescription of adalimumab will rely on therapists' decision and will be made independently to the inclusion of the patient in the PMOS. Adalimumab therapy has a well-established and well described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since the first approved indication in 2003 for Rheumatoid Arthritis in the EU.

Participants will be instructed to contact their physician in case of an emergency, or if at any time they are in need for a consultation.

8.0 Research Question and Objectives

We hypothesize that in axSpA patients treated with adalimumab an active supervised training is superior to standard of care physiotherapy in improving health-related outcomes.

To address this research question we will conduct a two-arm observational study with axSpA patients who, based on physicians' decision, are responding to adalimumab treatment and are eligible for active physiotherapy. Patients will be randomized to receive either active supervised and standardized training (AST group) or standard of care physiotherapy (SOC group).

The active supervised and standardized training consists of 24 units of exercise within 20 weeks and will be performed in certified FPZ training centers. After the 20-week training program, patients in the AST group who have still muscular deconditioning of Stage II or worse will be offered a subsequent training program consisting of 10 units within 8 to 10 weeks. The training concept is described in detail in Annex 1.

Standard of care physiotherapy as used here includes active as well as passive training and massages according to the physiotherapist discretion. The type of physiotherapy will be documented in the eCRF. Due to a lack of structured guidance in the treatment recommendations the quality and quantity of physiotherapy within the SOC arm will

not precisely be defined. Instead, the SOC arm will reflect the status quo of current physiotherapy treatment regime in Germany and thus will provide a real world comparison to generate real world evidence.

Health-related outcomes will be assessed at the Enrollment Visit (initiation of adalimumab treatment), at the Baseline Visit (after Randomization), after 3, 6, 9 and 12 month follow-up from baseline. For each follow-up time point a timeframe of ± 4 weeks will be acceptable.

The primary objective of this study is to compare active supervised training with standard of care physiotherapy in improving spinal mobility after 6 month from Baseline Visit in axSpA patients in context of adalimumab therapy.

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

Due to the non-interventional, observational character of the study, any action will be based on the physicians' decision due to analysis of axSpA patient data, which will reflect clinical routine. No additional diagnostic or monitoring procedures will be applied.

9.0 Research Methods

9.1 Study Design

Treatment of axSpA patients with adalimumab will be according to the local adalimumab product label and local standard of care, including timing of clinic visits, required laboratory tests and any other procedures required for appropriate therapy. Patients on adalimumab therapy have received the local patient information, and should be advised of the potential benefits and risks of adalimumab by their physicians as well as being instructed in injection techniques. Adalimumab will be obtained as commercially available medication. AbbVie will not provide the medication for this study.

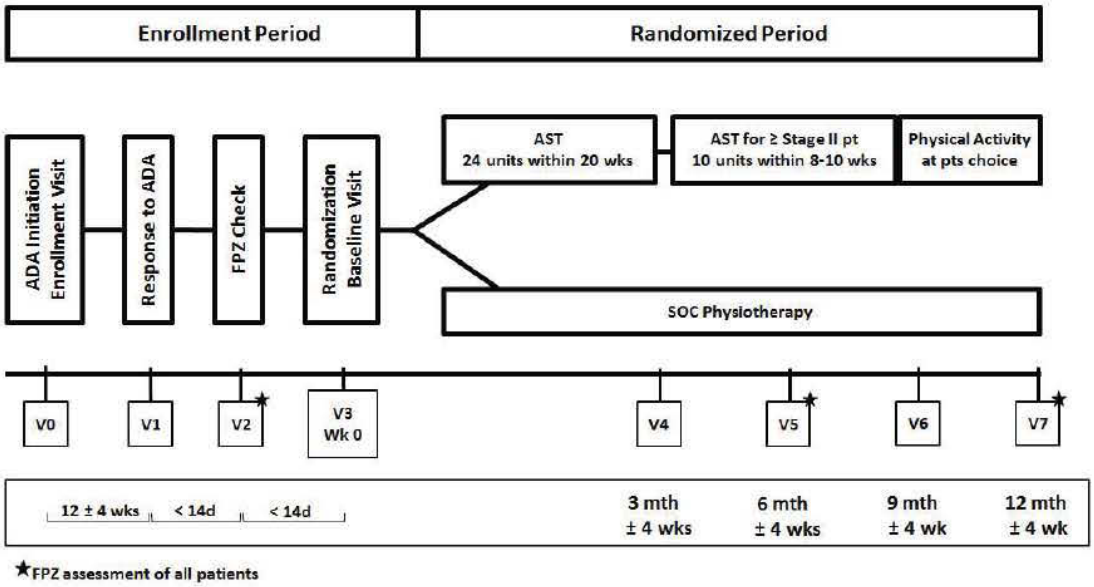
This protocol describes a post-marketing, observational study that will exploratively investigate the impact of active supervised training compared to standard of care physiotherapy in context of adalimumab treatment.

Adult axSpA patients initiating treatment with adalimumab based on current clinical practice criteria will be informed about the study. After written consent they will be enrolled in the study at the Enrollment Visit. Patients with sufficient response to adalimumab treatment within 12 +/- 4 weeks (as defined individually by the treating physician) and who will be eligible for active physiotherapy (according to the rheumatologist's and the physiotherapist's decision) will be randomized in an 1:1 ratio to receive either active supervised training (AST group) or standard of care physiotherapy (SOC group) (Fig.1). Randomization of the patients will be balanced regarding gender, age and disease activity (BASDAI).

Patients not eligible for FPZ training will be excluded from the study. Eligibility to participate in the study is based on the basic ability of the patient to undergo active physical exercise. The decision will be based on the physicians and the physiotherapist's discretion.

The observational period of the study will comprise a follow-up period of 12 month after Baseline Visit. An enrollment period of treatment initiation and response assessment for 3 to 5 month will precede Baseline Visit and Randomization (Fig. 1).

Figure 1: Study Design Schematic



Study procedures will be performed as outlined in the schematic presented Table 1.

Table 1 and Table 2: Study Activities

Table 1: Study Activities	**Start ADA (Enrollment Visit) V0**	**Response Assessment V1**	**FPZ Assessment V2**	**Randomization (Baseline Visit) V3**	**3 Month follow-up from baseline V4**
Patient Authorization	X				
Inclusion/Exclusion Criteria	X[1]	X[2]	X[3]		
Age, gender, body weight, height, smoking	X				
Social-, educational background	X				
Non-axSpA Medical/Surgical History	X				
axSpA Medical/Surgical History	X				
Disease duration	X				
Family history	X				
HLA-B27	X				
Comorbidities	X				
Prior axSpA- medication	X				
Current axSpA- medication	X	X		X	X
Concomitant medication	X	X		X	X
Type of regular physical exercise	X				
Type of physical therapy	X	X		X	X
Serious Adverse Events /Adverse Events	X	X	X	X	X
CRP or ESR / Blood Sampling as per routine	X	X		X	X
BASMI$_{lin}$	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
Fear avoidance behavior	X	X		X	X

questionnaire (FABq)					

1. Inclusion Criteria: Patients diagnosed with axSpA, aged at least 18 years; Prescription of adalimumab for treating axSpA according to the local product label; Patients must have signed written informed consent before starting any study-related assessments or procedures;
   Exclusion Criteria: Patients with poorly controlled medical condition(s), which in the opinion of the investigator, would put the subject at risk by participation in the protocol; Patients with total spinal ankylosis based on the investigators' assessments of available radiographs; Any prior treatment with a biologic DMARD is prohibited
2. Inclusion Criteria: Response to adalimumab therapy after 12 +/- 4 weeks (no therapy escalation or change in treatment regime is required due to rheumatologist's opinion); Eligible for active physiotherapy according to the rheumatologist
3. Inclusion Criteria: Eligible for active physiotherapy according to the physiotherapist (according to FPZ requirements)

Table 2: Study Activities Follow-up	**6 Month follow-up from baseline V5**	**9 Month follow-up from baseline V6**	**12 Month follow-up from baseline V7**
Comorbidities	X	X	X
Current axSpA- medication	X	X	X
Concomitant medication	X	X	X
Type of regular physical exercise	X	X	X
Type of physiotherapy	X	X	X
Serious Adverse Events /Adverse Events	X	X	X
CRP or ESR / Blood Sampling as per routine	X	X	X
BASMIlin	X	X	X
BASFI	X	X	X
ASAS-HI	X	X	X
ASDAS	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
Fear avoidance behavior questionnaire (FABq)	X	X	X

9.2 Setting

Approximately 510 patients with axSpA (ASAS Criteria 2009[16]) who receive adalimumab according to the local product label and who fulfill the study eligibility criteria will be enrolled. It is expected that the number of 510 patients treated with adalimumab is sufficient to meet the objectives of this PMOS. Approximately 50 rheumatologists will contribute to enroll eligible patients in this study.

Patients who consent to participate in the study will be observed for up to 12 month from baseline. Physicians should treat enrolled axSpA patients just as they treat axSpA patients in the routine clinical practice. Patients may discontinue adalimumab treatment or the study at any time for any reason. Following discontinuation of adalimumab, the patient will be treated in accordance with the investigator's best clinical judgment.

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

- SAE: reported to AbbVie within 24 hours of physician awareness
- Non serious AE: reported to AbbVie within 24 hours of physician awareness

Patients that end adalimumab treatment or start treatment on any other biologic marketed in the EU will be withdrawn from the study and will not be part of the primary analysis population.

If a patient withdraws or is lost to follow-up, every effort should be made to note such along with the reason for withdrawal in the electronic case report form (eCRF).

Inclusion Criteria

A patient will be eligible for study participation if he/she meets the following criteria:

- Patients diagnosed with axSpA (either AS or nr-axSpA), fulfilling the ASAS classification, aged at least 18 years

- Prescription of adalimumab for treating axSpA according to the local product label
- Eligibility for active physiotherapy according to the rheumatologist and physiotherapist
- Patients must have signed written informed consent before starting any study-related assessments or procedures

Exclusion Criteria

A patient will not be eligible for study participation if he/she meets any of the following criteria:

- Patients with total spinal ankylosis based on the investigators' assessments of available radiographs
- Patients who are not eligible for active supervised training or active physiotherapy at the discretion of the rheumatologist and/or the physiotherapist
- Patients with poorly controlled medical condition(s), which in the opinion of the investigator, would put the subject at risk by participation in the protocol
- Any prior treatment with a biologic DMARD is prohibited

9.3 Variables

Health-related outcomes will be assessed at the Enrollment Visit (initiation of adalimumab treatment), at the Baseline Visit (after Randomization), after 3, 6, 9 and 12 month follow-up from baseline. For each follow-up time point a timeframe of ± 4 weeks will be acceptable.

The primary outcome parameter is the improvement of spinal mobility after 6 month from Baseline Visit as measured by the Bath Ankylosing Spondylitis Metrology Index [BASMI] in the AST group as compared to SOC group.

BASMI is an objective measure to capture in detail the range of movement and spinal mobility. Its sensitivity is proven for the measurements of spinal mobility impairment during the stages of the axSpA disease course. Further, BASMI will provide an objective readout as it does not depend on PRO parameters and thus will be less confounded by psychosocial factors.

Importantly, relevant exercises of the established training concept developed by the AST provider directly correlate with four of the five BASMI measures. Hence, BASMI will be the optimal, objective and validated measure of choice to observe spinal mobility of the AST population vs the SOC population.

PROs were not chosen as primary outcome parameter as psychosocial factors render them less objective. Research has shown that patients with a high risk of depression and anxiety score higher in BASDAI, BASFI, EQ5D and ASDAS-CRP as well as in the overall pain score (VAS) and ASQoL. Nevertheless, besides somatic parameters, the accurate assessment of psychosocial risk factors, by the above mentioned appropriate questionnaires is of high importance. Therefore, the selected measures will be used.

Secondary outcome parameter will include the following:

- Spinal mobility – Evaluated by the Bath Ankylosing Spondylitis Metrology Index [BASMI]
- Physical Function – Evaluated by the BASFI NRS score (0 to 10)
- Overall functioning by ASAS Health Index (HI)
- Disease activity as measured by Bath AS Disease Activity Index (BASDAI)
- Percentage of patients achieving 50% improvement in BASDAI (BASDAI 50 response)
- Disease activity as measured by Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Percentage of patients in ASDAS inactive disease (ASDAS < 1.3)
- Percentage of patients with low disease activity (ASDAS < 2.1)
- Percentage of subjects with moderate disease activity (ASDAS ≥ 1.3 to < 2.1)
- Percentage of subjects with high disease activity (ASDAS ≥ 2.1 to < 3.5)
- Percentage of subjects with very high disease activity (ASDAS ≥ 3.5)

- ASDAS major improvement ($\Delta \geq 2.0$)
- ASDAS clinically important improvement ($\Delta \geq 1.0$)
- ASAS 20, ASAS 40, and ASAS Partial Remission
    - ASAS20 response: improvement of $\geq 20\%$ and absolute improvement of $\geq$ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains, with no deterioration in the remaining domain (defined as a worsening of $\geq 20\%$ and a net worsening of ≥ 1 unit)
        - Patient's Global Assessment – Represented by the PTGA-disease activity NRS score (0 to 10)
        - Pain – Represented by the patient's assessment of total back pain NRS score (0 to 10)
        - Function – Represented by the BASFI NRS score (0 to 10)
        - Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10])
    - ASAS40 response: improvement of $\geq 40\%$ and absolute improvement of $\geq$ 2 units (on a scale of 0 to 10) from Baseline in ≥ 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain Function as measured by Bath AS Functional Index (BASFI NRS)
    - ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20
- Patient's Global Assessment of Pain
- Patient's Assessment of Total Back Pain
- Patient's Assessment of Nocturnal Back Pain
- Work Ability Index (modified WAI)
- Fatigue (BASDAI question 1)
- Duration and severity of morning stiffness (mean of BASDAI questions 5 and 6)

Psychosocial risk factors

- Fear avoidance behavior (FABQ)

Other variables evaluated include:

- Comorbid conditions

- Concomitant medications:
  - Prior and concomitant non-biologic disease-modifying antirheumatic drugs (DMARDs)
  - Concomitant systemic glucocorticoids
  - Concomitant pain relief medications: analgesics, non-selective non-steroidal anti-rheumatic drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors

9.4 Data Sources

The reported data for the study will be available from the patient's file as well as the documentation done at the FPZ training center.

9.5 Study Size

Ciprian et al. (2013), Masiero et al. (2014) and Ygrit et al. (2013) show BASMI improvement of one point in populations receiving structured physiotherapy, compared to control groups (Liang et al. 2015). With the assumed detectable difference of one BASMI point, an assumed power of 80% and a standard deviation of 3.7 the sample size per arm is calculated to be 216 patients (total 432 patients).

Due to a complex enrolment flow, the long duration of the non-interventional study and the physical exposure of the patients we may expect a dropout rate of 15%, resulting in a total enrolment of 510 patients.

9.6 Data Management

Data for this study will be recorded in German by each participating center via an electronic data capture (EDC) system using a web-based eCRF with a unique subject ID code on a web-based encrypted platform. The participating site enters all data following pseudonymization. Data of clinical examination, diagnostic measures, laboratory assessments, findings and observations routinely performed in patients with

adalimumab therapy included in this cohort, will be transcribed by hand by the rheumatologist or study nurse from the source documents into the eCRF. And the source documents will be stored on site. Only data specified in the protocol will be entered into the eCRF. For each enrolled patient, the investigator or designee will create a new patient file in the eCRF and a unique patient number will be automatically allocated by the system. A comprehensive data validation program utilizing front-end checks in the eCRF will validate the data. Plausibility checks on defined limits and variable values will take place automatically. Automated checks for data consistency will be implemented; discrepancies need to be solved by the researcher in the eCRF before the module can be completed.

Follow-up on eCRF data for medical plausibility will be done by AbbVie medical personnel (or their representatives). Queries will be generated in the eCRF for online resolution at the site. The investigator or an authorized member of the investigator's staff will make any necessary data corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. The principal investigator will finally review the eCRFs for completeness and accuracy of available data and provide his or her electronic signature and date to the eCRFs as evidence thereof. In addition, a qualified representative of the AbbVie medical department who is obliged to maintain confidentiality will visit the site periodically to conduct quality assurance measures. This includes training staff before study initiation, answering questions and clarifying any queries. Source data verification may be organized in collaboration with study personnel.

Access to the EDC system will be provided for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (e.g. CD-ROM) and provided to the investigator as a durable record of the site's eCRF data. Original Questionnaires will be sent from the participating site to:

e.factum GmbH
Werner-von-Siemens-Straße 1

35510 Butzbach

[redacted]

9.7 Data Analysis

9.7.1 Analysis populations:

Safety set: all patients enrolled and received at least one treatment with Adalimumab

ITT set: all patients randomized

Per protocol set (PPS): all patients randomized and performed AST or SOC physiotherapy until 6 months without severe protocol violations

Note: Several per protocol sets might be defined according coherence with AST and SOC treatment, respectively. Those specific PPS will be defined in SAP.

9.7.2 Background and demographic characteristics:

Continuously scaled variables will be described by mean, standard deviation, median, min, max, Q1 and Q3. Categorical variables will be described by counts and percentages.

9.7.3 Analysis of primary endpoint:

The primary analysis will performed at ITT set.

The BASMI at 6 months (V5) will be analysed within an ANCOVA with treatment as fixed effect and baseline BASMI (V3) as covariate. The treatment effect will be reported with its 95%-confidence interval. In case prerequisites of ANCOVA are not given, according methods might be applied (transformation of data).

Note: The BASMI (BASMIlin) is continuously scaled, because it is the mean of 5 analog measures on a scale 0 - 10.

9.7.4 Analysis of secondary endpoints:

Continuously scaled variables with available baseline data will be analysed like the primary endpoint.

If baseline data are not available, 2-paired t-test will be applied.

The analysis of categorically scaled outcome variables by treatment will be performed by contingency tables. Related tests (□2-Test, Armitage trend test) will be performed. Binary variables will be analysed by logistic regression.

All treatment related effects will be reported with their 95% confidence interval.

9.7.5 Missing data and sensitivity analyses

(1)

Missing data within questionnaires (single items are missing) will be imputed questionnaire specific rules. If such rules does not exist, missing single items will be replaced by the mean or median (details: see SAP) of the other items of the respective patient at the specific visit, if no more than 25% of the items are missing. If more than 25% of items are missing, the whole score is set to missing.

(2)

One might expect that patients finish either the AST or the SOC physiotherapy for several reasons.

In case of less than 10% of missing data for primary outcome variable, the complete case analysis is efficient. In case of more missing data, the following approaches will be applied in the sense of sensitivity analyses.

First, the underlying mechanism will be investigated by logistic regression modelling (missing information y/n = f(baseline data, success of treatment between enrollment and baseline assessment)). In case of MCAR (missing completely at random) the

analysis will be performed at complete cases. In case of MAR (missing at random), multiple imputation might be applied in a sensitivity analysis. In case of MNAR (missing not at random) a specific analysis is not possible, and scenario assuming several drop-out scenario will be investigated. Such sensitivity analyses (e. g. last observation carried forward, baseline value is carried forward, missing AST will be imputed by respective SOC data) will be defined in statistical analysis plan.

9.7.6 Assessment of covariates

Within primary model further influencing variables (baseline data, data describing success of treatment between enrollment and baseline assessment) might be investigated. Details will be provided in SAP.

Centers could be regarded as random effects within these models (mixed models) to investigate homogeneity of the effects.

9.7.7 Safety data

Safety data will be described using the safety set. The data will be presented by severity, intensity, requirement of treatment, system organ class, causality, outcome, action taken.

9.7.8 Data review and SAP

Data will be investigated in a blinded data review meeting in terms of protocol violations and missing data. Consequences for analysis will be taken into account in the SAP.

Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions.

9.8 Quality Control

Prior to any study-related data being collected, patient authorization to use and/or disclose personal and/or health data will be obtained and will be reviewed and signed and dated by the patient and physician who administered the patient authorization. A copy of the signed patient authorization will be given to the patient and the original will be placed in the patient's medical record. A patient authorization for use/disclosure of data template will be provided.

Prior to the initiation of the study, rheumatologists and site personnel will be trained on the study and the FPZ concept (described in Annex 1). Training will include a detailed discussion of the protocol and study procedures (study design, patient flow, in- and exclusion criteria), patient reported outcomes (PRO) and procedure of data management (e.g. eCRF completion). FPZ personnel will be trained on medical background of axial spondyloarthritis, disease characteristics and peculiar features of patients' clinical condition in regards to physical exercise.

All data generated by the rheumatologist will be entered via the eCRF. All data generated by FPZ will be transferred to CRO and inserted into the respective patient eCRF. After entry of the data, computer logic checks will be run to check for inconsistent data.

9.9 Limitations of the Research Methods

9.10 Other Aspects

10.0 Protection of Human Subjects

This PMOS will be run in compliance with local laws and regulations (§4 German Drug Law, AMG). Notification/submission to the responsible regulatory authorities, Ethics Committee (EC), Health Insurance bodies and Competent Authorities (CAs) will be done as required by local laws and regulations.

The investigator is responsible to ensure that written informed consent to use and/or disclose patients' pseudomized health data will be obtained prior to patient inclusion.

To maintain patient confidentiality, no demographic data that can identify the patient will be collected (e.g. initials, date of birth) - only the patient age will be collected. In order to protect patient identity, a unique number will be assigned to each patient and related study recording.

11.0 Management and Reporting of Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 11.2.2). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 11.2.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

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

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

11.1.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event.

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

11.1.4 Serious Adverse Event Collection Period

Serious adverse and non-serious events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

11.1.5 Serious Adverse Event Reporting

Product-related events including Adverse Reaction Reporting

This is an observational research study not designed to identify or quantify a safety hazard relating to adalimumab.

If a patient reports a product-related event (e.g. suspected adverse reaction or product complaint) to his/her healthcare professional during the data collection period or the healthcare professional identifies a product-related event, which is considered related to adalimumab or any other AbbVie authorized product, the event should be reported to AbbVie. Any product-related events considered to be related to a non-AbbVie product should be reported in accordance with local laws and regulations to the relevant Regulatory Authority and/or drug marketing authorisation holder.

Patient Reported Outcome (PRO) data are not considered a potential source of adverse reactions. However, participating sites should review the PRO data and if a possible product-related event (including a suspected adverse reaction) is noted, the HCP must determine whether the event is related to adalimumab and if so, it should be reported to AbbVie.

In the event of a serious adverse event, the physician will:

- For events from patients using and AbbVie product - notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the event.
- For events from patients using a comparator product - notify the Marketing Application Holder (MAH) for the comparator product within 24 hours of the physician becoming aware of the event.

This protocol requires all SAEs and non-serious adverse events as outlined in protocol section 11.1.1 to be actively solicited.

The relevant AbbVie Pharmacovigilance contact details are specified below:

AbbVie Deutschland GmbH & Co. KG

Arzneimittelsicherheit (AMS) AbbVie Deutschland

Mainzer Straße 81

65189 Wiesbaden, Germany

[redacted]

11.1.6 Pregnancy Reporting

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 0 within 24 hours of the physician becoming aware of the pregnancy.

11.2 Product Complaint

11.2.1 Definition

A Product Complaint is any Complaint related to the biologic or drug component of the product or to the device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

11.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via

local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product and/or device should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

The relevant AbbVie Pharmacovigilance contact details see section 11.1.5.

12.0 Plans for Disseminating and Communicating Study Results

A final study report will be written. This report will contain a description of the objectives of the study, the methodology of the study and its results and conclusions. The completed eCRFs and the study report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this study may be published by AbbVie or by any one of the participating physicians after written agreement with AbbVie.

13.0 References

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14.0 Annex 1. Additional Information

14.1.1 The AST provider: FPZ therapy

The FPZ therapy is an evidence-based back pain therapy based on intensive, active and supervised training which focuses on back fitness, core strengthening and patient engagement.

The FPZ concept strictly follows principal physiological and innovative knowledge for training which is reflected by the historical term FPZ (Forschungs- und Präventionszentrum, engl. Research and Prevention Center) going back to the time when the concept has been developed.

According to the individual deconditioning status the patient will perform 10 or 24 sessions within three to four months. The training is offered in "certified" FPZ-training- or physiotherapy centers and will be conducted as machine based training with a defined sequence of exercises under accurate supervision of especially trained physiotherapists or exercise physiologists. The training machines are part of an especially developed and certified high-tech equipment which is based on standardized methodology and makes possible an exact monitoring and documentation of all exercises and other relevant patient parameters.

Therapists, being especially trained and continuously educated on the FPZ-concept, assess the patient and exactly monitor the performance of all exercises. Moreover they assess and positively influence psychosocial risk factors by offering an intense assistance and support for the patients.

By definition the FPZ therapy is an interdisciplinary evidence-based medical training concept for the treatment of back pain patients with

- functional backpain
- clear medical indication and
- advanced chronification of disease pattern (stadium I or II after Gerbershagen/Schmitt) and
- advanced deconditioning of the spine stabilizing musculature (stadium 3 or 4 after Denner).

From a medical perspective, the FPZ therapy represents an integrated functional back

pain therapy with the primary aim to recondition the patient. Being based on the bio-psycho-social model for back pain the FPZ therapy can firstly be applied in a predominantly curative way and subsequently in a secondary preventive way in order to stabilize the achieved success in the long run.

With help of the FPZ 4-level-diagnostics, consisting of

1. orthopedic diagnostics
2. structural diagnostics,
3. pain diagnostics and
4. functional diagnostics

it is ensured that only suitable patients enter the therapy
(= qualified suitability check and selection of back pain patients on the basis of medical necessity).
As could be demonstrated so far, the FPZ-concept on average cares for the achievement of the following parameters:

- Increase of maximum strength: +31%
- Increase of muscular performance: +67%
- Recovery of muscular dysbalances and asymmetries in >90% of cases within 6 months
- Pain reduction in > 70% of patients measured on a 0-10 NRS

Since its entrance into the health care market, the FPZ demonstrates high level effectiveness and a reliable safety profile for the treatment of back pain patients. Currently, the FPZ-concept represents the only working example for integrated health care in Germany and thus the concept can be prescribed by experienced physicians and is reimbursed by many sick-funds.

14.1.2 The FPZ therapy handbook (German)

Separate PDF document