

1.0

Title Page

**Clinical Study Protocol W15-679**

**Incorporating Amendments 1 and 2**

**STRIKE – Treating Patients with Early Axial  
Spondyloarthritis to Target – a 1 Year Randomized  
Controlled Study Taking an Intense Treatment  
Approach Versus Routine Treatment**

AbbVie  
Investigational  
Product:

Adalimumab

Date: 30 March 2017

Development Phase: 4

Study Design: This is a randomized, controlled, open-label, monocountry,  
multicenter study

EudraCT Number: 2015-005398-18

Investigators: Multicenter trial (Investigator information is on file at AbbVie)

Sponsor: AbbVie Deutschland GmbH & Co. KG (AbbVie)  
Mainzer Str. 81  
65189 Wiesbaden

Sponsor/Emergency  
Contact:



This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

**Confidential Information**

**No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.**

## 1.1 Protocol Amendment: Summary of Changes

### Previous Protocol Versions

Protocol	Date
Original	04-February-2016
Amendment 1	24-June-2016

### Amendment 2

The purpose of this amendment is to:

- Update [Section 1.2](#), Synopsis  
***Rationale:** Added change in BASMI<sub>lin</sub> to secondary objectives in Objectives and Criteria for Evaluation subsections to align with Section 5.3.1, Table 1 – Study Activities; increased the number of participating study sites to allow for faster enrollment; and aligned the Statistical Methods subsection with the respective wording concerning the safety analyses in Section 8.1.6 of the protocol.*
- Update [Section 5.1](#), Overall Study Design and Plan: Description, and [Section 5.5.1](#), Treatments Administered  
***Rationale:** Provided clarification regarding NSAIDs to be used in case of escalation to Escalation Step 2 due to intolerance to NSAID 2.*
- Update [Section 5.2.1](#), Inclusion Criteria  
***Rationale:** Removed statement concerning male contraception from inclusion criterion 9 to align with contraception requirements outlined in Section 5.2.4.*
- [Section 5.2.4](#), Contraception Recommendations  
***Rationale:** Aligned Section title and Section with updates in inclusion criterion concerning contraception as well as corresponding Section 5.2.4 in new protocol template.*
- [Section 5.3.1](#), Efficacy and Safety Measurements assessed and Flow Chart  
***Rationale:** Updated footer 1 in Table 1 – Study Activities for further clarification concerning MRI assessment in case of premature study discontinuation.*
- [Section 5.3.1.1](#), Study Procedures

*Aligned time point of 1<sup>st</sup> MRI (Screening) between Section 5.3, Table 1 - Study Activities and the text; provided further clarification on the IGRA test to be used for TB screening; updated study drug to study treatment in 'Medical and Surgical History' and 'Laboratory Analyses' subsections for further clarification; and clarified that the visit schedule will continue with the first dose of study treatment subsequent to completion of TB screening and prophylaxis (if applicable).*

- [Section 5.3.2.1](#), Collection of samples for analysis

**Rationale:** *Ensured alignment of the data points recorded during central laboratory sample collection with the eCRF (instead of with the sample requisition form).*

- [Section 5.3.3.2](#), Secondary Endpoints

**Rationale:** *Added change in BASMI<sub>lin</sub> to secondary objectives to align with Section 5.3.1, Table 1 – Study Activities.*

- [Section 6.1](#), Medical Complaints

**Rationale:** *Changed Section title from 'Adverse Events' to 'Medical Complaints' to align with new protocol template.*

- [Section 6.1.3](#), Relationship to Humira

**Rationale:** *Updated definitions of reasonable versus no reasonable possibility to align with new protocol template.*

- [Section 6.1.5](#), Adverse Event Reporting

**Rationale:** *Updated responsible safety contact due to change in AbbVie Pharmacovigilance team.*

- [Section 6.1.6](#), Pregnancy Reporting

**Rationale:** *Updated Section to align with new protocol template.*

- [Section 9.1](#), Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

**Rationale:** *Updated Section to align with new protocol template.*

- [Section 13](#), Completion of the Study

**Rationale:** *Updated Section to align with new protocol template.*

Changes to the specific sections of the protocol are shown in the redline version of the protocol using ~~strike-through red font for deletions~~ and red underlined for insertions.

A copy of this protocol amendment will be sent to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and the responsible Health Authority.

The changes described in this protocol amendment required IRB/IEC approval prior to implementation.

The changes will not affect the study population.

### **Amendment 1**

The purpose of this **amendment** was to:

- Update Section 1.2, Synopsis.

***Rationale:*** Aligned the Statistical Methods subsection with Section 8.1.6 of the protocol in view of the definition and collection period of treatment emergent adverse events.

- Update Section 1.3, List of Abbreviations.

***Rationale:*** Removed high sensitivity C-reactive protein (hs CRP) from the List of Abbreviations to reflect that C-reactive protein (CRP) will be assessed instead of hs CRP.

- Update Section 5.2.2, Exclusion criteria.

***Rationale:*** Amended the criteria upon Ethics Committee's request, to reflect that vulnerable patients are not eligible to participate in the study.

- Section 5.2.4, Contraception Recommendations.

***Rationale:*** Corrected the threshold concerning age limits for menopause to account for female subjects at 55 years of age.

- Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart.

***Rationale:*** Updated Table 1 (Study Activities), Table 2 (Clinical Laboratory Tests) and the Section text to reflect that CRP will be assessed instead of hs CRP; updated the Section text to clarify that Human Leukocyte Antigen-B27 (HLA-B27) does not have to be performed (again) in case of a rescreen or if a result of a previously documented HLA-B27 test is available; aligned the Section text with Table 1 to reflect that MRI assessments will be performed at Screening instead of Baseline, and to simultaneously provide instructions on the time points of the MRI assessments at

*Screening; and updated the Section text to provide more detailed clarification to subject numbering.*

- Updated Section 5.4.1, Discontinuation of Individual Subjects.

***Rationale:*** *Upon Ethics Committee's request, provided more detailed clarification on the reasons for premature study discontinuation of individual subjects by cross-referencing to Section 6.1.7.*

- Updated Section 5.4.2, Discontinuation of Entire Study.

***Rationale:*** *Upon Ethics Committee's request, provided more detailed clarification on the reasons for premature study termination.*

- Updated Section 5.6.3, Suitability of Subject Population.

***Rationale:*** *Corrected Section text for alignment with inclusion criterion 5 in Section 5.2.1.*

- Updated Section 6.1.3, Relationship to Humira.

***Rationale:*** *Updated the Section text to clarify that relationship to Humira will be assessed for all adverse events irrespective of their seriousness.*

- Updated Section 6.1.7, Toxicity Management.

***Rationale:*** *Amended Section text with information on management of selected laboratory abnormalities.*

- Updated Section 8.1.6, Safety Analysis.

***Rationale:*** *Amended Section text for alignment with Section 1.2 (Synopsis).*

- Updated Appendix C, Assessment of SpondyloArthritis International Society (ASAS) Axial Spondyloarthritis Criteria for Classification.

***Rationale:*** *Updated Appendix C for alignment with inclusion criterion 2 in Section 5.2.1.*

- Updated Appendix S, Berlin Magnetic Resonance Imaging (MRI) Score for the Spine and the Sacroiliac Joints.

***Rationale:*** *Updated Appendix S to correct the Grades in the Berlin Magnetic Resonance Imaging (MRI) Score assessed.*

## 1.2 Synopsis

<b>AbbVie Inc.</b>	<b>Protocol Number:</b> W15-679
<b>Name of Study Drug:</b> Adalimumab	<b>Phase of Development:</b> 4
<b>Name of Active Ingredient:</b> Adalimumab	<b>Date of Protocol Synopsis:</b> 30 March 2017
<b>Protocol Title:</b> STRIKE – Treating Patients with Early Axial Spondyloarthritis to Target – a 1 Year Randomized Controlled Study Taking an Intense Treatment Approach Versus Routine Treatment	
<b>Objectives:</b> The <b>Primary Objective</b> of this study is to compare a treat-to-target (T2T) intense treatment approach with a routine treatment approach (Standard of Care [SOC]) in reducing disease activity at Week 32 in patients with axial spondyloarthritis (axSpA). The <b>Secondary Objectives</b> are to compare a T2T intense treatment approach with SOC by assessing the following at Week 32 and Week 52: improvement of quality of life <ul style="list-style-type: none"> <li>• Quality of life by the European Quality of Life – 5 Dimension Questionnaire (EQ-5D)</li> <li>• Overall functioning by Assessment of Spondyloarthritis International Society (ASAS) Health Index (HI)</li> </ul> improvement of function <ul style="list-style-type: none"> <li>• Function – Represented by the Bath AS (Ankylosing Spondylitis) Functional Index (BASFI) Numerical Rating Scale (NRS) score (0 to 10)</li> </ul> improvement of work productivity <ul style="list-style-type: none"> <li>• Work Productivity and Activity Impairment – Axial Spondyloarthritis (WPAI-axSpA)</li> </ul> reducing inflammation <ul style="list-style-type: none"> <li>• Active inflammation as measured by magnetic resonance imaging of the sacroiliac joints and the spine (Berlin Magnetic Resonance Imaging [MRI] scores for the sacroiliac [SI] joints and spine)</li> <li>• C-reactive Protein</li> <li>• Erythrocyte sedimentation rate</li> </ul> reducing disease activity <ul style="list-style-type: none"> <li>• Disease activity as measured by Bath AS Disease Activity Index (BASDAI)</li> <li>• Percentage of subjects achieving 50% improvement in BASDAI (BASDAI 50 response)</li> <li>• Change from Baseline in disease activity measured by Ankylosing Spondylitis Disease Activity Score (ASDAS)</li> <li>• Percentage of subjects achieving ASDAS major improvement</li> <li>• Percentage of subjects achieving ASDAS clinically important improvement</li> <li>• Percentage of subjects in ASDAS inactive disease (ASDAS &lt; 1.3)</li> <li>• Percentage of subjects with low disease activity (ASDAS &lt; 2.1)</li> <li>• Percentage of subjects with moderate disease activity (ASDAS ≥ 1.3 to &lt; 2.1)</li> <li>• Percentage of subjects with high disease activity (ASDAS ≥ 2.1 to &lt; 3.5)</li> <li>• Percentage of subjects with very high disease activity (ASDAS ≥ 3.5)</li> </ul>	

**Objectives (Continued):**

- Percentage of subjects achieving ASAS 20, ASAS 40, and 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
- Change from Baseline in Patient's Global Assessment of Pain
- Change from Baseline in Swollen Joint Count (66 joints)
- Change from Baseline in Tender Joint Count (68 joints)
- Change from Baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- Change from Baseline in the Dactylitis count (0 – 20)
- Change from Baseline in BASMI<sub>lin</sub>
- Anterior uveitis

Other variables to be analyzed at various time points including Week 32 and Week 52:

- ASDAS course over time
- BASDAI course over time

Exploratory Objectives:

- Serum autoantibodies against cluster of differentiation 74 class II-associated invariant chain peptide (CD74 CLIP)
- Reduction of disease progression (as measured by MRI of the sacroiliac joints and the spine)

**Investigators:** Multicenter (Investigator information is on file at AbbVie).

**Study Sites:** Approximately 30 sites

**Study Population:** Adult subjects with a diagnosis of axSpA and disease duration less than 5 years

**Number of Subjects to be Enrolled:** Approximately 240

**Methodology:**

This is a Phase 4, multicenter, randomized, open-label, parallel-group study comparing an intensified T2T treatment approach with SOC.

The study duration will include a 42-day Screening period, a 52-week treatment period (treatment T2T according to randomization or SOC), and – only for subjects who receive study drug Humira but do not continue on commercially available Humira after the study – a 70 day follow-up phone call.

Subjects who have signed the informed consent and who fulfill all screening criteria will be randomized to receive either treatment following an intensified T2T approach (T2T group) or treatment according to SOC (following the local practice standards) (SOC group).

**T2T Group (Investigational Group):**

After randomization subjects are seen at Weeks 2, 4, 6, 8 and afterwards every 4 weeks up to Week 52.

Basic treatment will be started with a non-steroidal anti-inflammatory drug (NSAID). Treatment should be intensified (escalated) beginning at Week 4 if the ASDAS is  $\geq 2.1$  (escalation step 1). Treatment escalation is planned to be initiated at Week 4, if needed and further escalation is planned at Week 8, if needed (escalation step 2). However, if not required at Week 8, treatment can be escalated at every visit thereafter if the ongoing treatment is not sufficiently efficacious and the escalation step 2 has not yet been reached. Treatment escalation steps are as follows:

**Methodology (Continued):**

T2T Group (Investigational Group) (Continued):

- Basic treatment (NSAID 1): Treatment will be started with any NSAID and given for 4 weeks at full anti-inflammatory dose. If at Week 2 ASAS 20 response is not achieved, subjects may early escape to Escalation Step 1. If the chosen NSAID cannot be continued due to intolerance, escalation to the next escalation step is possible at any time point. If basic treatment is well tolerated and sufficiently efficacious the subject will be continued on this treatment.
- Escalation step 1 (NSAID 2): Treatment will be changed to a second NSAID if after 4 weeks of treatment the first NSAID is not sufficiently efficacious ( $ASDAS \geq 2.1$ ) and/or not tolerated. The second NSAID will be given for 4 weeks. Early escape is possible if after 2 weeks no ASAS 20 response is achieved. In this case treatment can be switched to escalation step 2 after 2 weeks of NSAID 2. If the chosen NSAID cannot be continued due to intolerance, escalation to the next escalation step is possible at any time point. If NSAID 2 treatment is well tolerated and sufficiently efficacious the subject will be continued on this treatment.
- Escalation step 2 (Combination with adalimumab): In case of failure of NSAID 2 ( $ASDAS \geq 2.1$  after 4 weeks of NSAID 2) the treatment will be intensified by switching to the combination of NSAID and adalimumab 40 mg s.c. every other week (eow). Escalation step 2 can be initiated at Week 4 visit at the earliest if early escape is chosen during Basic Treatment and during NSAID 2.

SOC Group (Reference Group):

After randomization, subjects will receive treatment according to local practice standards. Subjects are seen at Weeks 12, 24, 32, and 52.

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

**Main Inclusion:**

1. Subjects must have signed written informed consent before starting any study-related assessments or procedures.
2. Diagnosis of axSpA (either ankylosing spondylitis or non-radiographic axSpA) and fulfilling the ASAS classification criteria for axSpA.
3. Subjects aged  $\geq 18$  years.
4. Disease duration  $< 5$  years.
5. Subjects must have a baseline disease activity as defined by having an  $ASDAS \geq 2.1$  or a  $BASDAI \geq 4$ .
6. Subjects must be either NSAID-naïve or had not been treated with the maximal recommended dose during the last 2 weeks prior to the Baseline Visit.
7. Subjects must never have failed a NSAID taken at maximal recommended dose for 2 weeks or more.

**Main Exclusion:**

1. Contraindications for NSAIDs or Tumor Necrosis Factor (TNF) blocker according to local labeling.
2. If entering the study on concomitant NSAIDs, subjects taking the maximal recommended dose during the last 2 weeks prior to the Baseline Visit or have failed or developed intolerance to a NSAID taken at maximal recommended dose for 2 weeks or more at any time.



**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Exclusion (Continued):**

3. Prior exposure to any anti-TNF therapy; any biologic therapy with a potential therapeutic impact on SpA, or subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit.

**Investigational Product:** Adalimumab

**Dose:** 40 mg eow

**Mode of Administration:** s.c.

**Reference Therapy:** Local Standard of Care

**Duration of Treatment:**

Subjects will be treated for 52 weeks receiving either treatment according to the T2T intensified treatment scheme or SOC. Study drug will only be administered in the T2T group. Length of exposure will depend on individual necessity for intensifying treatment. The maximal duration of treatment with adalimumab is up to 48 weeks.

**Criteria for Evaluation:**

**Efficacy:**

The primary efficacy endpoint is the clinical disease activity at Week 32 as measured by the percentage of subjects in ASDAS inactive disease (ASDAS < 1.3).

Secondary efficacy endpoints include the following at Week 32 and Week 52:

- Quality of life by the European Quality of Life – 5 Dimension Questionnaire (EQ-5D)
- Work Productivity and Activity Impairment – axSpA (WPAI-axSpA)
- Overall functioning by ASAS HI
- Disease activity as measured by BASDAI
- Percentage of subjects achieving 50% improvement in BASDAI (BASDAI 50 response)
- Function – Represented by the BASFI NRS score (0 to 10)
- Change from Baseline in 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, ASAS 40, and ASAS Partial Remission
- Active inflammation as measured by magnetic resonance imaging of the sacroiliac joints and the spine (Berlin MRI scores for the SI joints and spine)
- Change from Baseline in Physician's Global Assessment of Disease Activity
- Change from Baseline in Patient's Global Assessment of Disease Activity

## Criteria for Evaluation (Continued):

### Efficacy (Continued):

- Change from Baseline in Patient's Global Assessment of Pain
- Change from Baseline in Swollen Joint Count (66 joints)
- Change from Baseline in Tender Joint Count (68 joints)
- Change from Baseline in the MASES
- Change from Baseline in the Dactylitis count (0 – 20)
- Change from Baseline in BASMI<sub>lin</sub>
- Anterior uveitis

Other variables to be analyzed at various time points including Week 32 and Week 52:

- C-reactive Protein
- Erythrocyte sedimentation rate
- ASDAS course over time
- BASDAI course over time

Exploratory endpoints:

- Serum autoantibodies against CD74 CLIP
- Reduction of disease progression (as measure by MRI of the sacroiliac joints and the spine)

### Pharmacokinetic:

N.A.

### Safety:

Screening assessments will include medical history, vital signs, physical examination, and clinical laboratory tests. The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, assessments of vital signs, physical examination and laboratory tests.

## Statistical Methods:

### Efficacy:

The primary efficacy endpoint is the response rate of clinical disease activity at Week 32 as measured by the percentage of subjects with ASDAS inactive disease ( $ASDAS < 1.3$ ) in the two treatment arms. Subjects with missing data at Week 32 subjects will be counted as non-responders (non-responder imputation). The null hypothesis states that there is no difference in response rates between the intensified T2T arm and the SOC arm; the alternative hypothesis is that the response rates are different. The response rates will be tested using a two-sided Pearson's chi square test with  $\alpha = 0.05$ . The Fisher's exact test will be applied, if  $\geq 25\%$  of the cells in the frequency table have expected counts less than 5.

All statistical tests which will be performed for secondary endpoints are only of exploratory nature and no adjustment for multiple comparisons is planned. Discrete secondary efficacy variables will be compared between the two treatment arms using Pearson's chi-square (or Fisher's exact test if more appropriate) and continuous secondary variables will be compared between the treatment arms using an analysis of covariance method adjusting for the corresponding baseline values. Descriptive statistics will also be provided for primary and secondary variables.

## **Statistical Methods (Continued):**

### **Pharmacokinetic:**

N.A.

### **Safety:**

Safety analyses will be carried out using the safety population, which includes all subjects who received treatment for axSpA after randomization Treatment-emergent AEs and serious AEs (SAEs), which include pre- and post-treatment SAEs, will be summarized and reported.

Treatment-emergent AEs are defined as AEs that begin either on or after the Baseline Visit up to the end of the study (including for the T2T arm, up to 70 days after the last dose of the study medication, except for those subjects that initiate adalimumab therapy not supplied in the context of the clinical trial after the end of study participation). The number and percent of subjects experiencing AEs will be tabulated by system organ class and Medical Dictionary for Drug Regulatory Activities (MedDRA<sup>®</sup>) preferred term. In addition, a summary of treatment-emergent AEs by severity and relationship to study drug will be presented. Serious, severe, or life-threatening AEs and those that lead to premature study discontinuation will be listed and described.

Mean change in vital signs and laboratory variables at each visit as compared to Baseline will be summarized for all treated subjects, and compared between treatment groups using a one way Analysis of Variance (ANOVA). The last evaluation on or prior to the Baseline visit will be used as baseline for all analyses. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 3 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variables.

### **Sample Size:**

Based on available data from previous studies it is assumed that ASDAS inactive disease could be reached by 40% in the T2T group versus 20% in the control group. In total  $2 \times 90$  evaluable subjects are necessary to detect with 80% power an increase in ASDAS inactive disease at Week 32 from 20% in the SOC arm to 40% in the intensified T2T arm, if a two sided Fisher's exact test is applied. If the Pearson chi-square test instead of the Fisher's exact test can be applied (see Section 8.1.4.1), then only  $2 \times 83$  subjects are necessary.

Assuming that about 18% of the randomized subjects will drop out prior to Week 32 and have to be counted as non-responder the assumed ASDAS inactive disease rate will be diluted to 16.4% in the SOC arm and 32.8% in the intensified T2T arm. The necessary sample size for this scenario (intent to treat [ITT] population) is  $2 \times 109$  subjects for the chi-square test and  $2 \times 119$  subjects for the Fisher's exact test. In summary,  $2 \times 120$  subjects should be randomized.

### 1.3 List of Abbreviations and Definition of Terms

#### Abbreviations

6-MP	6-mercaptopurine
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANOVA	Analysis of variance
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
axSpA	Axial spondyloarthritis
AZA	Azathioprine
BASDAI	Bath AS Disease Activity Index
BASFI	Bath AS Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacillus Calmette-Guérin
BD	Behçet's disease
CD	Crohn's disease
CD74 CLIP	Cluster of differentiation 74 class II-associated invariant chain peptide
CDC	Centers for Disease Control and Prevention
CRA	Clinical Research Associate
CRP	C-reactive Protein
CS	Clinically significant
csDMARD	conventional systemic disease-modifying anti-rheumatic drug
CTC	Common toxicity criteria
CXR	Chest X-ray
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
ECG	Electro Cardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture

---

EMA	European Medicines Agency
Eow	Every other week
EQ-5D	European Quality of Life – 5 Dimension
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GPRD	Global Pharmaceutical Research and Development
HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HI	Health Index
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen-B27
IBP	Inflammatory back pain
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IGRA	Interferon-Gamma Release Assay
IMP	Investigational Medicinal Product
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
JIA	Juvenile idiopathic arthritis
LSMEAN	Least square mean values
LOCF	Last observation carried forward
MASES	Maastricht AS Enthesitis Score

---

---

MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NCS	Not clinically significant
nr-axSpA	Non-radiographic axial spondyloarthritis
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drug
NYHA	New York Heart Association
PA	Posterior-anterior
PCR	Polymerase chain reaction
POR	Proof of receipt
PPD	Purified Protein Derivative
PsA	Psoriatic arthritis
PTGA	Patient's Global Assessment
RA	Rheumatoid arthritis
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous
SI	Sacroiliac
SJC	Swollen Joint Count
SOC	Standard of Care
SpA	Spondyloarthritis
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2T	Treat-to-target
TB	Tuberculosis
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
UC	Ulcerative colitis
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
WPAI	Work Productivity and Activity Impairment

---

## 2.0

## Table of Contents

<b>1.0</b>	<b>Title Page .....</b>	<b>1</b>
1.1	Protocol Amendment: Summary of Changes .....	2
1.2	Synopsis .....	6
1.3	List of Abbreviations and Definition of Terms.....	12
<b>2.0</b>	<b>Table of Contents.....</b>	<b>15</b>
<b>3.0</b>	<b>Introduction .....</b>	<b>20</b>
3.1	Axial Spondyloarthritis .....	20
3.2	Current Treatments .....	20
3.3	Adalimumab Overview .....	23
3.4	Safety Information .....	24
3.5	Considerations on the Best Outcome Parameter for a Treat-to-Target (T2T) Approach in axSpA.....	24
3.6	Rationale for the Study .....	27
3.7	Differences Statement .....	28
3.8	Benefits and Risks.....	28
<b>4.0</b>	<b>Study Objective.....</b>	<b>29</b>
<b>5.0</b>	<b>Investigational Plan .....</b>	<b>29</b>
5.1	Overall Study Design and Plan: Description .....	29
5.2	Selection of Study Population.....	35
5.2.1	Inclusion Criteria .....	35
5.2.2	Exclusion Criteria .....	36
5.2.3	Prior and Concomitant Therapy.....	39
5.2.3.1	Prior Therapy .....	40
5.2.3.2	Concomitant Therapy.....	41
5.2.3.3	Prohibited Therapy.....	42
5.2.4	Contraception Recommendations .....	43
5.3	Efficacy, Pharmacodynamic, and Safety Assessments/Variables .....	45
5.3.1	Efficacy and Safety Measurements Assessed and Flow Chart .....	45
5.3.1.1	Study Procedures .....	53
5.3.2	Measurement of Autoantibodies Against CD74 CLIP .....	67
5.3.2.1	Collection of Samples for Analysis .....	67

5.3.2.2	Handling/Processing of Samples for the Detection of Autoantibodies Against CD74 CLIP .....	68
5.3.2.3	Disposition of Samples for the Detection of Autoantibodies Against CD74 CLIP .....	68
5.3.3	Efficacy Endpoints.....	69
5.3.3.1	Primary Efficacy Endpoint .....	69
5.3.3.2	Secondary Endpoints .....	69
5.3.3.3	Exploratory Endpoints .....	71
5.3.4	Safety Variables .....	71
5.4	Removal of Subjects from Therapy or Assessment.....	71
5.4.1	Discontinuation of Individual Subjects.....	71
5.4.2	Discontinuation of Entire Study.....	73
5.5	Treatments.....	73
5.5.1	Treatments Administered.....	73
5.5.2	Identity of Investigational Product.....	75
5.5.2.1	Packaging and Labeling .....	75
5.5.2.2	Storage and Disposition of Study Drug .....	75
5.5.3	Method of Assigning Subjects to Treatment Groups.....	76
5.5.4	Selection and Timing of Dose for Each Subject.....	76
5.5.5	Blinding.....	77
5.5.5.1	Blinding of Investigational Product .....	77
5.5.6	Treatment Compliance.....	77
5.5.7	Drug Accountability.....	77
5.6	Discussion and Justification of Study Design.....	78
5.6.1	Discussion of Study Design and Choice of Control Groups.....	78
5.6.2	Appropriateness of Measurements.....	79
5.6.3	Suitability of Subject Population .....	79
5.6.4	Selection of Doses in the Study .....	79
<b>6.0</b>	<b>Complaints .....</b>	<b>80</b>
6.1	Medical Complaints .....	80
6.1.1	Definition .....	81
6.1.1.1	Adverse Event .....	81
6.1.1.2	Serious Adverse Events .....	82



6.1.2	Adverse Event Severity.....	83
6.1.3	Relationship to Humira .....	83
6.1.4	Adverse Event Collection Period.....	84
6.1.5	Adverse Event Reporting .....	85
6.1.6	Pregnancy.....	86
6.1.7	Toxicity Management .....	87
6.2	Product Complaint .....	88
6.2.1	Definition .....	88
6.2.2	Reporting.....	89
<b>7.0</b>	<b>Protocol Deviations.....</b>	<b>89</b>
<b>8.0</b>	<b>Statistical Methods and Determination of Sample Size .....</b>	<b>90</b>
8.1	Statistical and Analytical Plans.....	90
8.1.1	Analysis Population .....	90
8.1.2	Statistical and Analytical Plan .....	91
8.1.3	Analysis of Demographic Data and Baseline Disease Characteristics.....	92
8.1.4	Statistical Analysis of Efficacy .....	92
8.1.4.1	Analysis of Primary Efficacy Endpoint .....	92
8.1.4.2	Analysis of Secondary Efficacy Endpoints.....	93
8.1.4.3	Other Exploratory Analyses.....	94
8.1.5	Pharmacokinetic Analyses .....	94
8.1.6	Safety Analysis .....	94
8.1.7	Interim Analysis.....	94
8.2	Determination of Sample Size .....	95
8.3	Randomization Methods .....	96
<b>9.0</b>	<b>Ethics.....</b>	<b>96</b>
9.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB) .....	96
9.2	Ethical Conduct of the Study .....	97
9.3	Subject Information and Consent.....	97
<b>10.0</b>	<b>Source Documents and Case Report Form Completion .....</b>	<b>98</b>

---

10.1	Source Documents .....	98
10.2	Case Report Forms.....	99
<b>11.0</b>	<b>Data Quality Assurance .....</b>	<b>100</b>
<b>12.0</b>	<b>Use of Information.....</b>	<b>100</b>
<b>13.0</b>	<b>Completion of the Study .....</b>	<b>101</b>
<b>14.0</b>	<b>Investigator's Agreement.....</b>	<b>102</b>
<b>15.0</b>	<b>Reference List .....</b>	<b>103</b>

## List of Tables

Table 1.	Study Activities.....	46
Table 2.	Clinical Laboratory Tests.....	59
Table 3.	Identity of Investigational Products .....	75
Table 4.	Specific Toxicity Management Guidelines for Abnormal Laboratory Values.....	88

## List of Figures

Figure 1.	Study Design Schematic .....	31
Figure 2.	Adverse Event Collection .....	84

## List of Appendices

Appendix A.	Responsibilities of the Clinical Investigator .....	109
Appendix B.	List of Protocol Signatories.....	111
Appendix C.	Assessment of SpondyloArthritis International Society (ASAS) Axial Spondyloarthritis Criteria for Classification .....	112
Appendix D.	Features of Spondyloarthritis .....	113
Appendix E.	Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation .....	114
Appendix F.	Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Numerical Rating Scale (NRS).....	115

---

Appendix G.	Patient's Global Assessment of Disease Activity, Numerical Rating Scale (NRS).....	117
Appendix H.	Tender and Swollen Joint Counts .....	118
Appendix I.	Linear Bath Ankylosing Spondylitis Metrology Index (BASMI <sub>lin</sub> ).....	120
Appendix J.	Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).....	122
Appendix K.	Bath Ankylosing Spondylitis Functional Index (BASFI), Numerical Rating Scale (NRS).....	123
Appendix L.	Physician's Global Assessment of Disease Activity, Numerical Rating Scale (NRS).....	126
Appendix M.	Patient's Assessment of Nocturnal Back Pain, Numerical Rating Scale (NRS) .....	127
Appendix N.	Patient's Assessment of Total Back Pain, Numerical Rating Scale (NRS) .....	128
Appendix O.	Patient's Global Assessment of Pain, Numerical Rating Scale (NRS) .....	129
Appendix P.	Assessment of Spondyloarthritis International Society (ASAS) Health Index (HI) .....	130
Appendix Q.	Work Productivity and Activity Impairment Questionnaire: Axial Spondyloarthritis, V2.0 (Work Productivity and Activity Impairment [WPAI]: Axial Spondyloarthritis).....	133
Appendix R.	European Quality of Life – 5 Dimension (EQ-5D) (United States [US] English Version).....	135
Appendix S.	Berlin Magnetic Resonance Imaging (MRI) Score for the Spine and the Sacroiliac Joints.....	138
Appendix T.	70-Day Follow-Up Call – Sample .....	139
Appendix U.	Injection Instructions – Sample Pre-Filled Syringe .....	140
Appendix V.	Subject Dosing Diary Sheet (Sample) .....	157
Appendix W.	Subject NSAID Dosing Diary Sheet (Sample) .....	160
Appendix X.	Nonsteroidal Anti-Inflammatory Drug (NSAID) Intake Score .....	162
Appendix Y.	Recommended Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) to Treat Axial Spondyloarthritis .....	163

---

## **3.0 Introduction**

### **3.1 Axial Spondyloarthritis**

The term axial spondyloarthritis (axSpA) covers both patients with non-radiographic axSpA (nr-axSpA) and radiographic axSpA (the latter also termed ankylosing spondylitis [AS]). New classification criteria have been developed in 2009 by the Assessment in Spondylo-Arthritis international Society (ASAS) for axSpA which have already been applied in several treatment trials of patients with nr-axSpA or for the whole group of axSpA patients.<sup>1</sup> The prevalence of axSpA has been estimated to be between 0.2 and 1.9%, strongly dependent on the Human Leukocyte Antigen-B27 (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.<sup>2</sup> The new classification criteria and related diagnostic algorithm make an early diagnosis and treatment now possible because the occurrence of structural bony damage (radiographic sacroiliitis), which can take years to develop, is no longer mandatory.

### **3.2 Current Treatments**

According to the ASAS and European League Against Rheumatism (EULAR) recommendations, nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of therapy in symptomatic patients with axSpA.<sup>3</sup> Tumor necrosis factor alpha (TNF $\alpha$ )-blocking agents (TNF-blockers) are recommended in active axSpA with predominant axial manifestations if patients are still active after starting an NSAID therapy or if there are contraindication for an NSAID therapy. However, conventional DMARDs are not effective for the treatment the axial component of spondyloarthritis (SpA). In case of peripheral arthritis and/or enthesitis local glucocorticosteroid injections can be considered.<sup>3</sup> Currently NSAIDs and TNF-blockers are the only effective and approved drugs for the treatment of axSpA.

Recently, similar to previous 'treat to target' (T2T) recommendations for rheumatoid arthritis (RA),<sup>4</sup> T2T recommendations for the whole group of SpA including patients with

axSpA and psoriatic arthritis have been developed.<sup>5</sup> Key statements are that a major treatment target should be clinical remission/inactive disease of musculoskeletal involvement and that clinical remission/inactive disease is defined as the absence of clinical and laboratory evidence of significant inflammatory disease activity. However, axSpA treatment targets and treatment escalation strategies have not been identified and validated in a prospective study.

Thus, the question arises how such an aim can be achieved in patients with axSpA. The following data are currently available on a potential escalation strategy for the treatment of axSpA.

#### NSAIDs:

NSAIDs play a crucial role in the treatment of axSpA as NSAIDs are very effective drugs to treat signs and symptoms of AS patients, have a dose-dependent efficacy, have the ability to lower elevated C-reactive protein (CRP) levels and importantly seem to have a disease-modifying effect as has recently been shown in prospective studies.<sup>6-8</sup>

Furthermore, in early axSpA treatment with NSAIDs a state of Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (and 35.3% ASAS partial remission) can be reached in about 20% of patients, and also a reduction of active inflammation as detected by magnetic resonance imaging (MRI).<sup>9</sup> To facilitate and harmonize axSpA treatment with NSAIDs, ASAS has developed a NSAID equivalent score providing for each NSAID the dosage equivalent to 150 mg diclofenac together with the maximum dose used in axSpA.<sup>10</sup> However, a T2T approach for NSAIDs therapy in axSpA has not been investigated so far.

#### TNF-Blocker Treatment:

Numerous clinical trials have shown a clear efficacy of TNF-blocker treatment in axSpA. TNF-blockers are the treatment of choice in patients with axSpA and predominant axial manifestation after failure of NSAIDs in both established AS and nr-axSpA.<sup>11-13</sup>

However, it is not clear whether a combination therapy of TNF-blockers plus NSAIDs would be superior to TNF-blocker alone.

In a recently performed trial (INFAST), 51.4% of patients with early axSpA with a disease duration of < 3 years reached a status of ASDAS inactive disease during combination treatment with a TNF-blocker and a full dose of a NSAID (compared to 19.6% of patients who reached ASDAS inactive disease during NSAID monotherapy, as mentioned above). The corresponding figures for reaching ASAS partial remission were 61.9% and 35.3%, respectively.<sup>9</sup>

#### T2T Experience in RA:

In RA it has been shown that patients in whom treatment is intensified according to clearly defined treatment goals have a better outcome, both change scores and status scores have been proposed.<sup>14-17</sup>

The better outcome was defined here as a lower disease activity which could be reached during conventional systemic disease-modifying anti-rheumatic drug (csDMARD) therapy (without TNF-blocker) in CAMERA<sup>14</sup> (RA patients with disease duration < 1 year, 2 year follow-up), TICORA<sup>15</sup> (RA patients with disease duration < 5 years, 18 month follow-up) or the TNF-blocker trial by Schipper et al<sup>16</sup> (RA with disease duration < 1 year, 1 year follow-up) and the Dutch BeST study<sup>17,18</sup> by Goekoop-Ruiterman and co-workers (RA with disease duration < 2 years, 1 year follow-up). In most of these studies the primary outcome parameter was remission and/or low disease activity; functional status and radiographic progression after 1.5 – 2 years were secondary outcome parameters. A tight control, target-oriented therapy was typically superior to Standard of Care (SOC).

#### Treat to Target Experience in Patients with Spondyloarthritis

The recently published T2T recommendations in spondyloarthritis define remission or low disease activity as the treatment target.<sup>5</sup> These recommendations are largely based upon expert consensus, built on experience in RA patients and defined a research agenda.

Recently, the TICOPA trial assessed treatment escalation with conventional DMARDs followed by TNF-blocker therapy in patients with psoriatic arthritis, which was superior to the SOC for most outcome parameters.<sup>19,20</sup> Currently, no trials have evaluated whether a targeted treatment approach and combination of anti-TNF therapy with NSAIDs provides superior outcomes in patients with axSpA.

### **3.3 Adalimumab Overview**

Adalimumab (the TNF-blocker used in this study) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF- $\alpha$  but not to lymphotoxin- $\alpha$  (TNF- $\beta$ ).

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (CRP and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved for the treatment of subjects with RA in the United States (US) in December 2002 and in the European Union (EU) in September 2003. In addition adalimumab is approved for the treatment of patients with early RA, polyarticular juvenile idiopathic arthritis (JIA) (4 to 17 years of age), psoriatic arthritis (PsA), AS, Crohn's disease (CD), Ulcerative colitis (UC), and Psoriatic arthritis (PsA) in the EU, the US, and many other countries worldwide. Adalimumab is also approved for the treatment of

patients with polyarticular JIA (2 to < 4 years of age), pediatric CD, and nr-axSpA in the EU and several other countries, as well as intestinal Behçet's disease (BD) in Japan. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

### **3.4 Safety Information**

Adalimumab therapy has a well-established and well described safety profile based on extensive postmarketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in a Food and Drug Administration (FDA)-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in patients who are 30 years old or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event (AE) Reporting.

### **3.5 Considerations on the Best Outcome Parameter for a Treat-to-Target (T2T) Approach in axSpA**

The current ASAS recommendations only give limited guidance regarding a sufficient response for a TNF-blocker treatment: a responder is defined as a patient who shows a 50% improvement of the Bath AS Disease Activity Index (BASDAI) or an absolute change of at least 2 points after 12 weeks.<sup>21</sup>

Thus, in axSpA – in contrast to RA – only relative treatment targets (change scores) for TNF-blocker treatment recommendations have been proposed until now. There are several potential outcome parameters in the treatment of axSpA such as patient reported



outcomes (PROs) including the BASDAI and Bath AS Functional Index (BASFI), but also objective parameters of inflammation such as CRP and active inflammation on MRI.

There is ongoing discussion about the role of the BASDAI for measuring disease activity in axSpA as it has the limitations of being only a subjective patient-reported outcome parameter and it shows a poor correlation with objective parameters of disease activity such as CRP or inflammation on MRI.<sup>21</sup> CRP has the advantage that it is an objective measure of disease activity. Furthermore, CRP has been shown to be a predictor for a major response during TNF-blocker treatment<sup>22-24</sup> and a predictor for radiographic progression both in the sacroiliac joints<sup>25</sup> and in the spine.<sup>26</sup> Active inflammation on MRI can add valuable information in terms of disease activity. However, MRI cannot be performed routinely on every visit (feasibility problem).

The more recently introduced ASDAS combines both patient reported outcomes and an objective disease parameter represented by an acute phase reactant (CRP or ESR).<sup>27</sup>

The ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. As a continuous measure of disease activity, the ASDAS can be used to measure both relative improvement between 2 timepoints and also patient status at a single visit. The ASDAS was first published online in July 2008, since this time the ASDAS has undergone additional validation<sup>28-32</sup> and has emerged as the measurement tool recommended by experts in assessing axSpA disease activity. Furthermore, it is now recommended that the treatment goal should be to achieve remission (or low disease activity) in SpA patients.<sup>5</sup>

For the following reasons ASDAS is an appropriate measurement tool to determine inactive disease and clinical trial results for this outcome are important to provide to physicians who treat patients with axSpA:

The ASDAS has proven to be a highly discriminatory tool for the detection of clinically meaningful differences in clinical studies.<sup>33,34</sup>

The ASDAS has superior psychometric properties and is more sensitive to change as compared to previously existing tools used to measure disease activity in SpA.<sup>33</sup>

The ASDAS better reflects spinal inflammation, which is a hallmark of axSpA, than other composite measures due to inclusion of an acute phase reactant (ESR or CRP).<sup>35</sup>

ASDAS is the recommended outcome measure for a T2T paradigm<sup>36</sup> and importantly ASDAS inactive disease and MRI-remission have more overlap compared to ASAS partial remission and MRI-remission<sup>37</sup> with ASDAS also demonstrating a significant association with radiographic progression in the spine.<sup>38</sup>

Thus, the ASDAS seems currently to be the best outcome parameter to be applied in a T2T approach in axSpA. At least disease activity as measured by ASDAS of  $\geq 2.1$  will be used as the indicator for need to intensify treatment in this study.

An ASDAS of  $< 1.3$  (which represents ASDAS inactive disease) will be used as the primary outcome parameter.

#### ASDAS Data from Other Studies/Cohorts:

Published ranges for disease activity states as defined by the ASDAS are:  $< 1.3$  for "inactive disease";  $\geq 1.3$  to  $< 2.1$  for "moderate disease activity";  $\geq 2.1$  to  $\leq 3.5$  for "high disease activity" and  $> 3.5$  for "very high disease activity."<sup>33</sup> Ramiro et al showed in an analysis of the OASIS cohort<sup>24</sup> that disease activity, as measured by ASDAS, is longitudinally associated with radiographic progression in AS. Vastesaeger et al investigated whether using an ASDAS of  $\geq 2.1$  instead of a BASDAI of  $\geq 4.0$  would be a better cut-off for the initiation of a TNF-blocker treatment. He analyzed cross-sectional data of the Spanish Regisponser registry (n = 1161) and found that 66.4% of these patients had an ASDAS of  $\geq 2.1$ , while only 50.9% of the same patients had a BASDAI of  $\geq 4.0$ .<sup>39</sup>

Fagerli et al in the NOR-DMARD cohort also compared whether using an ASDAS of  $\geq 2.1$  is more accurate than a BASDAI of  $\geq 4.0$  for the start of a TNF-blocker treatment.<sup>40</sup> Their analysis showed that the majority of patients fulfilled both criteria, however, 16.6% of the patients had an ASDAS of  $\geq 2.1$  and a BASDAI  $< 4$  (meaning that 16.6% would have been missed by the BASDAI eligibility criterion), and these patients responded similarly well to TNF-blocker treatment compared to a BASDAI cut-off (about 18% showed an ASDAS major improvement and about 50% reached ASDAS inactive disease).<sup>40</sup> The ASDAS was found to be applicable also in subgroups without elevated CRP and without peripheral joint swelling. At the 3-month follow-up of the NOR-DMARD cohort after initiation of a TNF-blocker treatment 33.6% of patients reached a status of ASDAS inactive disease.

In the German Spondyloarthritis Inception Cohort (GESPIC),<sup>41</sup> which is a prospective observational cohort including AS patients with a disease duration of  $< 10$  years in Year 6, (which was chosen here because all patients had potentially full access to TNF-blocker treatment), 54.5% of AS patients had an ASDAS  $\geq 2.1$ . Among these patients only 14.5% were on TNF-blocker treatment (unpublished data).

### 3.6 Rationale for the Study

So far in axSpA no clear treatment targets have been proposed, and there is a lack of evidence regarding the advantage of a T2T approach combining NSAID therapy with TNF-blockers. Indeed, data from observational cohorts indicate that a substantial number of patients in routine care are not sufficiently treated with about 50% of AS patients having a BASDAI  $\geq 4$  and about 20% of patients having a BASDAI  $\geq 6$  in the GESPIC cohort. Data from the DESIR cohort also shows that not the full anti-inflammatory dose of NSAID is taken as measured by the ASAS-NSAID-Score of 42% – 55%.<sup>42</sup> To monitor disease activity and the effectiveness of the therapy the BASDAI is currently used in routine care.<sup>43</sup>

Therefore, in this study an intensified T2T treatment approach comprising clearly defined treatment targets and cut-offs for treatment escalation shall be investigated in comparison to SOC treatment.

### **3.7 Differences Statement**

This is the first adequately powered study to evaluate the efficacy and safety of an intensified T2T treatment approach using clearly defined treatment targets and cut-offs for treatment escalation and escalating to combination treatment with a NSAID and adalimumab (if needed) versus routine treatment according to local SOC in subjects with axSpA.

### **3.8 Benefits and Risks**

There is an unmet medical need for the treatment of axSpA. A T2T paradigm has been proposed but no data are available to support this treatment approach. In this study, a T2T treatment scheme escalating to combination treatment with one NSAID and adalimumab (if needed) is investigated. The utility of TNF blockade with adalimumab in axSpA has been established in randomized controlled trials which demonstrated a safety profile similar to that observed in the extensive clinical and post-marketing experience of adalimumab in a wide range of disease states. The safety profile of adalimumab in this and other approved indications is well established. Adverse events in the categories of autoimmunity, demyelinating disorders, congestive heart failure, gastrointestinal disorders, hematologic events, hepatic events, hypersensitivity, immunosuppression, infections, malignancies, respiratory thoracic and mediastinal disorders, and vascular disorders have been observed with adalimumab therapy. The investigator is referred to the current Investigator's Brochure where additional and more detailed information regarding potential risks and benefits of adalimumab can be found. The potential benefit of the proposed study in axSpA is that it is designed to evaluate the efficacy and safety of an intensified T2T treatment approach to achieve and maintain remission of disease. As axSpA is associated with considerable pain, reduction in health-related quality of life, and work impairment it would be beneficial to know if using an intensified T2T treatment

approach remission of disease may be achieved and better maintained – while at the same time keeping acceptable adverse events rates – as compared to when using SOC.

In a randomized controlled trial comparing tight control of early psoriatic arthritis (TICOPA)<sup>19,20</sup> with standard care an increased rate of adverse events (AEs) were seen in the tight control arm: eight serious AEs in the tight control arm compared to two in the SOC arm; altogether 622 AEs (in 97% of patients) in the tight control arm versus 249 (in 80% of patients) with SOC.

## **4.0 Study Objective**

The primary objective of this study is to compare a T2T intense treatment approach with a routine treatment approach (SOC) in reducing disease activity at Week 32 in patients with axSpA.

The secondary objectives are to compare a T2T intense treatment approach with SOC by assessing improvement of quality of life, function and work productivity as well as reducing inflammation (as measured by MRI, CRP, ESR) and disease activity. Exploratory endpoints include investigating serum autoantibodies against CD74 CLIP and reduction of disease progression as measured by MRI of the sacroiliac joints and the spine.

## **5.0 Investigational Plan**

### **5.1 Overall Study Design and Plan: Description**

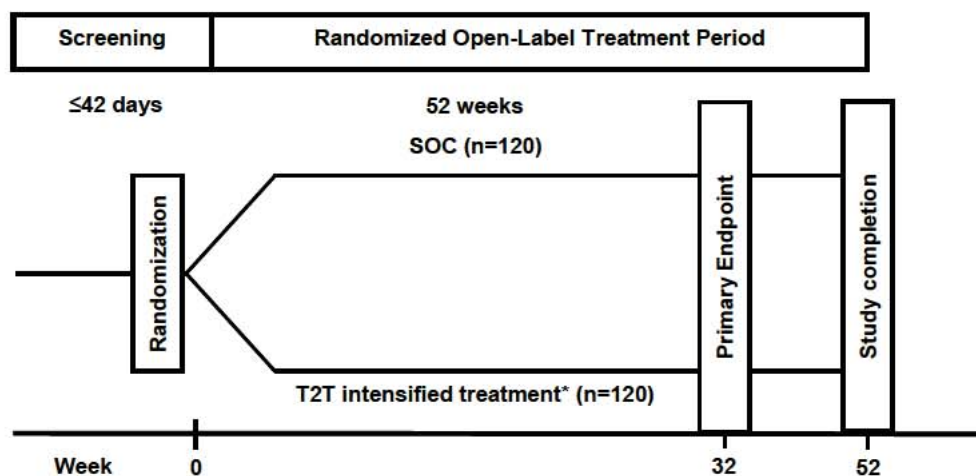
This is a Phase 4, multicenter, randomized, open-label, parallel-group study comparing an intensified T2T treatment approach with SOC. The study duration per subject may include a 42-day Screening period, a 52-week treatment period (T2T according to randomization or treatment SOC), and a 70 day follow-up period which will be completed by a phone call.

Subjects who have signed the informed consent and who fulfill all screening criteria will be randomized to receive either treatment following an intensified T2T approach (T2T

group) or treatment according to SOC (following the local practice standards) (SOC group).

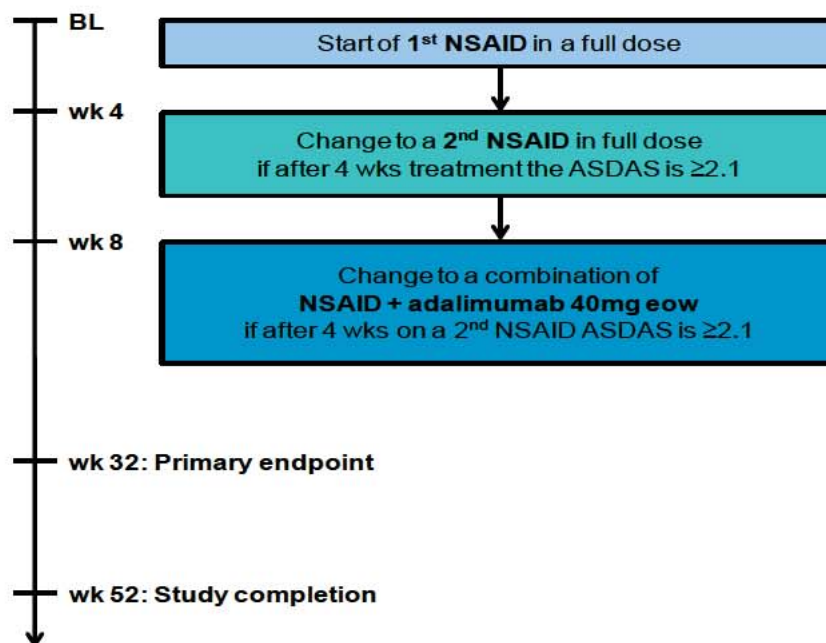
The study design schematic is presented in Figure 1.

**Figure 1. Study Design Schematic**



\* Escalation schedule for the T2T intensified treatment see below.

#### Escalation in the T2T intensified treatment group



Early escape after 2 wks NSAIDs intake: In case of no ASAS 20 response or intolerance switch to next escalation step (2<sup>nd</sup> NSAID/NSAID+ADA)

### **Screening Period:**

Within 42 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Table 1.

Subjects who initially screen-fail for the study may be permitted to re-screen following re-consent. The reason for screen failure will be captured in the appropriate Electronic Case Report Forms (eCRFs). All screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study; however, a subject should only be re-screened once for this study upon prior agreement with AbbVie Clinical Monitor. Subjects who have screen-failed previously and do not have a reasonable chance of meeting the inclusion/exclusion criteria should not be re-screened. If the subject had completed initial screening evaluation assessments including HLA-B27, Antinuclear Antibody (ANA), Magnetic Resonance Imaging (MRI) or electrocardiogram (ECG), these tests will not need to be repeated during re-screening provided the conditions noted in Section 5.3 are met and no more than 3 months (90 days) have passed for the ECG and no more than 42 days for the MRI. There is no need to redraw the HLA-B27 or ANA if results from the initial screening are available.

### **Treatment Period:**

This period will begin at the Baseline Visit (Day 1) and will end at the Week 52 visit. At the Baseline Visit, subjects who have signed the informed consent and meet the eligibility (all of the inclusion and none of the exclusion) criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled and randomized in a 1:1 ratio to receive either intensified T2T treatment or SOC treatment. Study physician and patients might be aware of the allocated treatment group. However, an influence of the SOC treatment based upon knowledge and potential benefits/risks in the intensified T2T treatment arm is not expected based on experience of other T2T-Studies like TICOPA.<sup>20</sup>



T2T Group (Investigational Group):

After randomization, subjects are seen at Weeks 2, 4, 6, 8 and afterwards every 4 weeks up to Week 52.

Basic treatment will be started with a NSAID. Treatment should be intensified (escalated) beginning at Week 4 if the ASDAS is  $\geq 2.1$  (escalation step 1). Treatment escalation is planned to be initiated at Week 4 if needed and further escalation is planned at Week 8 if needed (escalation step 2). However, if not required at Week 8, treatment should be escalated at every visit thereafter if the ongoing treatment is not sufficiently efficacious (ASDAS is  $< 2.1$ ) and the last escalation step has not yet been reached. Treatment escalation steps are as follows:

Basic Treatment (NSAID 1): Treatment will be started with any NSAID at full anti-inflammatory dose (see Appendix Y). If at Week 2 ASAS 20 response is not achieved, subjects may early escape to Escalation Step 1. If the chosen NSAID cannot be continued due to intolerance escalation to the next Escalation Step is possible at any time point. If Basic Treatment is well tolerated and ASDAS is  $< 2.1$  the subject will be continued on this treatment.

Escalation Step 1 (NSAID 2): Treatment will be changed to a second NSAID if after 4 weeks of treatment the first NSAID is not sufficiently efficacious (ASDAS  $\geq 2.1$ ) and/or not tolerated. The second NSAID will be given for 4 weeks. Early escape is possible if after 2 weeks no ASAS 20 response is achieved. In this case treatment can be switched to escalation step 2 after 2 weeks of NSAID 2. If the chosen NSAID cannot be continued due to intolerance, escalation to the next escalation step is possible at any time point. In that case, adalimumab may be combined with the second or – if deemed required by the treating physician – the first NSAID used (provided escalation from Basic Treatment to Escalation Step 1 did not occur due to any safety issues related to NSAID 1 therapy). If NSAID 2 treatment is well tolerated and sufficiently efficacious the subject will be continued on this treatment.

---

Escalation Step 2 (Combination with adalimumab): At Week 8 in case of failure of NSAID 2 (ASDAS  $\geq 2.1$  after 4 weeks of NSAID 2) the treatment will be intensified by switching to the combination of NSAID and adalimumab 40 mg s.c. every other week (eow). Escalation step 2 can be initiated at Week 4 visit at the earliest if early escape is chosen during Basic Treatment and during NSAID 2.

Before initiating Escalation Step 2 additional screening testing for hepatitis B and tuberculosis (TB) is required, as described in Section 5.3.1 and Table 1. If a subject is diagnosed with latent TB prophylactic treatment must be given. The subject must not receive adalimumab before completing at least 1 month of prophylactic anti-TB chemotherapy. If a subject is diagnosed with active hepatitis B (acute or chronic) the subject is not eligible to receive adalimumab and should discontinue from the study.

In case of peripheral arthritis and/or enthesitis: intra-articular injections of glucocorticosteroids are permitted at any time point and will be recorded in the concomitant medication electronic Case Report Form (eCRF).

SOC Group (Reference Group):

After randomization, subjects will receive treatment according to local practice standards. NSAIDs should be used according to ASAS recommendations (see Appendix Y) in a full dose. Unlike in the T2T group, the treating physician is blinded for the ASDAS calculated by the eCRF. Subjects are seen at Weeks 12, 24, 32 52 or if they discontinue early from the study.

T2T Group and SOC Group:

Subjects that end study participation early will have a Discontinuation Visit. Subjects of the T2T group who were on treatment with study drug adalimumab during the study but do not continue on commercially available Humira after discontinuation from the study will have a follow-up phone call approximately 70 days after the last visit within the Treatment Period (i.e., Week 52 visit or early Discontinuation Visit) to obtain information on any new or ongoing AEs.

Subjects who prematurely discontinue from the study should complete the procedures outlined for the Discontinuation Visit in Table 1 as soon as possible and preferably prior to the administration of new therapies.

The study is designed to enroll approximately 240 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

## **5.2 Selection of Study Population**

### **5.2.1 Inclusion Criteria**

1. Subjects must have signed written informed consent before starting any study-related assessments or procedures.
2. Diagnosis of axSpA (either AS or nr-axSpA) (see Appendix D) and fulfilling the ASAS classification criteria for axSpA (see Appendix C).
3. Subjects aged  $\geq 18$  years.
4. Disease duration  $< 5$  years.
5. Subjects must be either NSAID-naïve or had not been treated with the maximal recommended dose during the last 2 weeks prior to Baseline (see Appendix X).
6. Subjects must never have failed a NSAID taken at maximal recommended dose for 2 weeks or more.
7. Subjects must be disease-modifying anti-rheumatic drug (DMARD)-naïve except for methotrexate (MTX), sulfasalazine (SSZ), azathioprine (AZA), and 6-mercaptopurine (6-MP).
8. Subjects must have baseline disease activity as defined by having an ASDAS  $\geq 2.1$  or a BASDAI  $\geq 4$ .
9. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for Women of Childbearing Potential practicing at least one protocol

specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 150 days after the last dose of study drug.

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 20 weeks after the last dose of study drug, to practice the protocol specified contraception (Section 5.2.4).

10. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Baseline Visit.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

11. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, and a 12-lead ECG performed at Screening.
12. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
13. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

#### **Rationale for Inclusion Criteria**

- |         |  |
|---------|--|
| 1 – 9   | To select the appropriate subject population for this study    |
| 11 – 12 | To increase subject compliance potential                       |
| 13      | In accordance with the harmonized Good Clinical Practice (GCP) |

#### **5.2.2 Exclusion Criteria**

A subject will be excluded from the study if he/she meets any of the following criteria:

1. Contraindication for NSAIDs or TNF blocker according to local labeling.

- 
2. Subject has a medical condition precluding an MRI (e.g., magnetic activated implanted devices – cardiac pace-maker, insulin pump, neurostimulators, etc. and metallic devices or fragments in the body).
  3. Subject has active inflammatory bowel disease.
  4. Prior exposure to any anti-TNF therapy; any biologic therapy with a potential therapeutic impact on SpA, or subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit.
  5. If entering the study on concomitant NSAIDs, subjects taking the maximal recommended dose during the last 2 weeks prior to the Baseline Visit or have failed or developed intolerance to a NSAID taken at maximal recommended dose for 2 weeks or more at any time (see Appendix Y).
  6. Subject on opioid analgesics or use of marijuana within 14 days prior to the Baseline Visit.
  7. If entering the study on concomitant oral corticosteroids, subject has not been on stable dose of prednisone ( $\leq 10$  mg per day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
  8. Subject has been treated with intra-articular joint injection(s) or spinal/paraspinal injection(s) of corticosteroids in the preceding 28 days prior to the Baseline Visit.
  9. Subject has undergone spinal surgery within 2 months prior to Baseline or subject has been diagnosed with a spinal condition that may interfere with study assessments (i.e., disc herniation, degenerative spine disease, etc.) in the opinion of the investigator.
  10. Subject has a history of fibromyalgia or inflammatory arthritis of a different etiology other than SpA (e.g., rheumatoid arthritis, systemic lupus erythematosus, polyarticular or systemic juvenile idiopathic arthritis).

11. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
12. Known hypersensitivity to adalimumab or its excipients as stated in the label.
13. Known intolerance of NSAID treatment that does not allow use of at least two different NSAIDs at full anti-inflammatory dose (see Appendix Y).
14. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
15. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).
16. Subjects with any active viral infection that based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study.
17. Hepatitis B: Hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the hepatitis B virus (HBV)-DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab)/hepatitis B surface antibody (HBs Ab) positive subjects (see Section 5.3.1.1).
18. Chronic recurring infections or active TB.
19. History of moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
20. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma or localized carcinoma in situ of the cervix.
21. Positive pregnancy test at Screening or Baseline.
22. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 150 days after the last dose of study drug.

23. Male subject who is considering fathering a child or donating sperm during the study or for approximately 150 days after the last dose of study drug.
24. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
25. History of clinically significant drug or alcohol abuse in the last 12 months.
26. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
27. Any vulnerable subject (e.g., person kept in detention, or dependent from the Sponsor, Investigator or study site)

The Investigator should contact the AbbVie Medical Monitor identified in Section 6.1.5 if there are any questions regarding inclusion and exclusion criteria and subject eligibility.

#### **Rationale for Exclusion Criteria**

1 – 24, 26	To avoid medical conditions, medications or procedures that may compromise subject safety and the ability to make causality assessments relative to adalimumab
25	To increase subject compliance potential
27	In accordance with GCP and to comply with legal requirements

### **5.2.3 Prior and Concomitant Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of Screening, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate eCRF. Treatment for axSpA will be recorded in a separate section of the eCRF. NSAIDs administered to a subject for treatment of axSpA following the T2T intensified schedule will be recorded on the appropriate eCRF page.

The AbbVie Study Designated Physician identified in Section 6.1.5 (Adverse Event Reporting) should be contacted if there are any questions regarding concomitant or prior therapies.

In addition for subjects aged  $\leq 30$  with a reported malignancy adverse event, prior exposure to, or current use of, anti-neoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications in these categories used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

**Medication Categories:**

- corticosteroids
- immunosuppressants
- biologic agents
- anti-neoplastics
- other

**5.2.3.1 Prior Therapy**

All prior drug therapies for axSpA, since initial diagnosis, must be recorded on the source documents and on the appropriate eCRF along with the dates of first and last dose, maximum dosage taken, route of administration and reason for discontinuation, if known.

For each subject that is screened for the study, any other medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) taken at the time of Screening through the end of



the study must be recorded on the appropriate eCRF along with the date(s) of administration, reason for use, dosage, route and frequency.

### **5.2.3.2 Concomitant Therapy**

In case of peripheral arthritis and/or enthesitis: (intra-articular) injection of glucocorti-costeroids are permitted at any time point.

#### T2T Group

Treatment for axSpA will be recorded in a separate section of the eCRF. NSAIDs administered to a subject for treatment of axSpA following the T2T intensified schedule should be recorded in the eCRF as "T2T-NSAID," adalimumab should be recorded as study drug.

Each vaccine and all medications except study drug and T2T-NSAIDs, administered to a subject during the study should be recorded in the eCRF as a concomitant medication.

All non-drug therapies administered to a subject during the study should be recorded in the eCRF as a concomitant medication.

#### SOC Group

All medications administered to a subject for treatment of axSpA following the local SOC schedule should be recorded in the eCRF as "for axSpA."

Each vaccine and all medications except "for axSpA," administered to a subject during the study should be recorded in the eCRF as a concomitant medication.

All non-drug therapies administered to a subject during the study should be recorded in the eCRF as a concomitant medication.

### 5.2.3.3 Prohibited Therapy

#### T2T Group

The following are prohibited medications during the study:

- All biologic therapy with a potential therapeutic impact on SpA including but not limited to the following:
  - Infliximab (Remicade<sup>®</sup>);
  - Etanercept (Enbrel<sup>®</sup>);
  - Ustekinumab (Stelara<sup>®</sup>);
  - Natalizumab (Tysabri<sup>®</sup>);
  - Anakinra (Kineret<sup>®</sup>);
  - Abatacept (Orencia<sup>®</sup>);
  - Rituximab (Rituxan<sup>®</sup>);
  - Tocilizumab (Actemra<sup>®</sup>);
  - Golimumab (Simponi<sup>®</sup>);
  - Efalizumab (Raptiva<sup>®</sup>);
  - Certolizumab (Cimzia<sup>®</sup>);
  - Belimumab (Benlysta<sup>®</sup>);
  - Infliximab biosimilar(s) (Remsima<sup>®</sup>, Inflectra<sup>®</sup>);
  - Etanercept biosimilar(s);
  - Secukinumab (Cosentyx<sup>®</sup>).
- Live vaccines (during the study and for 70 days after the last dose of study drug Humira).
- Rifampin/Pyrazinamide combination.
- Anti-retroviral therapy.
- All oral DMARDs other than MTX, SSZ, AZA (permitted for inflammatory bowel disease only), or 6-MP (permitted for inflammatory bowel disease only).
- Opioid analgesics (other than tramadol or codeine) or marijuana, except as medical indicated for an AE.

- Any investigational drug of chemical or biologic nature.

Subjects may have to be discontinued from the study if any of the above prohibited medications are used during the study.

#### SOC Group

During the study (after randomization) no medication is explicitly prohibited by the study protocol. Investigators should follow the labeling of the medications administered and record them as required in the eCRF.

### **5.2.4 Contraception Recommendations**

If female, subject must be either postmenopausal defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.  
OR
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).  
OR
- Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 150 days after the last dose of study drug:
  - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Baseline Visit.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Baseline Visit.
  - Bilateral tubal occlusion/ligation.

- 
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
  - Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success and is the sole sexual partner of the women of childbearing potential (WOCBP) trial participant.
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 1 month prior to Baseline Visit.
  - Male or female condom with or without spermicide.
  - Cap, diaphragm or sponge with spermicide.
  - A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If a male subject is either surgically sterile (vasectomy with medical assessment confirming surgical success) or has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If a male subject is sexually active with female partner(s) of childbearing potential, he must agree from Baseline Visit through 20 weeks after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, male subject agrees not to donate sperm from Baseline Visit through 20 weeks after the last dose of study drug.

### **5.3 Efficacy, Pharmacodynamic, and Safety Assessments/Variables**

#### **5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart**

Subjects will be allowed a visit window of  $\pm 7$  days for all study visits.

If a subject has an out of window visit, the next visit should occur as originally scheduled based on the date of the Baseline Visit.

In subjects of the T2T group, HBV screening, TB screening and chest X-ray (CXR) will be performed before Escalation Step 2 is initiated (before adalimumab is administered). If a subject is diagnosed with latent TB the subject has to undergo a minimum of 1 month of anti-TB prophylaxis before Escalation Step 2 can be initiated. In this case the time until the next visit will be counted from the start of adalimumab; e.g., if a subject starts TB prophylaxis at Week 8 visit and initiates Escalation Step 2 after receiving 2 months of prophylaxis, i.e., 16 weeks after Baseline, the next visit (nominal Week 12 visit) will be postponed by these 2 months (to 20 weeks after Baseline). All subsequent visits will be postponed accordingly, e.g., Week 16 visit to 24 weeks after Baseline.

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

**Table 1. Study Activities**

T2T Group Activity	SCR (≤ 42 D)	BL <sup>a</sup> (D1)	Randomized Open-Label Treatment Period																Disc. <sup>b</sup> Visit <sup>b</sup>	70-Day F/U Call
			Week(s) (from D1) (1 wk Equals 7 Days)																	
			2	4	6	8	12	16	20	24	28	32	36	40	44	48	52			
Informed Consent	x																			
Inclusion/Exclusion Criteria	x	x <sup>c</sup>																		
Medical/Surgical History	x	x <sup>c</sup>																		
Vital Signs/Weight/Height <sup>d</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Anterior Uveitis	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
12-Lead ECG	x <sup>e</sup>																			
Chest X-Ray			x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>				
TB Screening (IGRA)			x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>	x <sup>f</sup> x <sup>f</sup>				
Pregnancy Test	x <sup>g</sup>	x <sup>h</sup> x <sup>h</sup>																	x	
Chemistry and Hematology	x	x <sup>i</sup> x <sup>i</sup>	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urinalysis <sup>j</sup>	x	x <sup>i</sup>	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	
HLA-B27	x <sup>e</sup>																			
Anti-dsDNA Antibodies	x <sup>e</sup>																			
HBV Screening	x		x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>	x <sup>k</sup> x <sup>k</sup>				
ESR	x	x <sup>i</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
CRP	x	x <sup>i</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Antibodies against CD74 CLIP		x															x		x	
MRI of the Spine and SI Joints	x <sup>e</sup>																		x <sup>l</sup>	

**Table 1. Study Activities (Continued)**

T2T Group Activity	SCR (≤42 D)	BL <sup>a</sup> (D1)	Randomized Open-Label Treatment Period														Disc. Visit <sup>b</sup>	70-Day F/U Call
			Week(s) (from D1) (1 wk Equals 7 Days)															
			2	4	6	8	12	16	20	24	28	32	36	40	44	48	52	
TJC/SJC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BASMI <sub>lin</sub>					X			X		X						X	X	
BASFI					X			X		X						X	X	
MASES		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dactylitis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Disease Activity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's Assessment of Nocturnal Back Pain NRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's Assessment of Total Back Pain NRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient's Global Assessment of Pain NRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ASAS HI		X				X			X							X	X	
EQ-5D		X				X			X							X	X	
WPAI-axSpA		X				X			X							X	X	
Prior and Concomitant Therapy Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Recording of NSAID: substance, dose, patient compliance (diary)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Recording of Study Drug: dose and patient compliance (diary)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

**Table 1. Study Activities (Continued)**

T2T Group Activity	SCR (≤ 42 D)	BL <sup>a</sup> (D1)	Randomized Open-Label Treatment Period																Disc. Visit <sup>b</sup>	70-Day F/U Call
			Week(s) (from D1) (1 wk Equals 7 Days)																	
			2	4	6	8	12	16	20	24	28	32	36	40	44	48	52			
Monitor AEs	x <sup>m</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x <sup>n</sup>		
Treatment Escalation Decision			x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>	x <sup>o</sup>				
Enrollment/Randomization		x																		
Study drug administration			x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>	x <sup>p</sup>			



**Table 1. Study Activities (Continued)**

SOC Group Activity	SCR (≤ 42 D)	BL <sup>a</sup> (D1)	Randomized Open-Label Treatment Period					Disc. Visit <sup>b</sup>
			Time of Visit (Weeks from D1) (1 wk Equals 7 Days)					
			Week 12	Week 24	Week 32	Week 52		
Informed Consent	x							
Inclusion/Exclusion Criteria	x	x <sup>c</sup>						
Medical/Surgical History	x	x <sup>c</sup>						
Vital Signs/Weight/Height <sup>d</sup>	x	x	x	x	x	x	x	x
Anterior Uveitis	x	x	x	x	x	x	x	x
Physical Exam	x	x	x	x	x	x	x	x
12-Lead ECG	x <sup>e</sup>							
Pregnancy Test	x <sup>g</sup>	x <sup>h</sup>				x		x
Chemistry and Hematology	x	x <sup>i</sup>	x	x	x	x	x	x
Urinalysis	x	x <sup>i</sup>	x	x	x	x	x	x
HLA-B27	x <sup>e</sup>							
Anti-dsDNA Antibodies	x <sup>e</sup>							
HBV Screening	x							
ESR	x	x <sup>i</sup>	x	x	x	x	x	x
CRP	x	x <sup>i</sup>	x	x	x	x	x	x
Antibodies against CD74 CLIP		x			x	x	x	x
MRI of the Spine and SI Joints	x <sup>e</sup>					x	x <sup>j</sup>	x <sup>j</sup>
TJC/SJC		x	x	x	x	x	x	x
BASDAI	x	x	x	x	x	x	x	x

**Table 1. Study Activities (Continued)**

SOC Group Activity	SCR (≤ 42 D)	BL <sup>a</sup> (D1)	Randomized Open-Label Treatment Period				Disc. Visit <sup>b</sup>
			Time of Visit (Weeks from D1) (1 wk Equals 7 Days)				
			Week 12	Week 24	Week 32	Week 52	
BASMI <sub>lin</sub>		X			X	X	X
BASFI		X			X	X	X
MASES		X		X	X	X	X
Dactylitis		X		X	X	X	X
Physician's Global Assessment of Disease Activity		X		X	X	X	X
Patient's Global Assessment of Disease Activity		X		X	X	X	X
Patient's Assessment of Nocturnal Back Pain NRS		X		X	X	X	X
Patient's Assessment of Total Back Pain NRS		X		X	X	X	X
Patient's Global Assessment of Pain NRS		X		X	X	X	X
ASAS HI		X		X	X	X	X
EQ-5D		X		X	X	X	X
WPAI-axSpA		X		X	X	X	X
Prior and Concomitant Therapy Assessment	X	X		X	X	X	X
Assessment of SOC Treatment for axSpA: Recording of substances, dose, frequency		X		X	X	X	X
Monitor AEs	X <sup>m</sup>	X		X	X	X	X
Enrollment/Randomization		X					

Ada = Adalimumab; BL = Baseline; D = Day; Disc. Visit = Discontinuation Visit; F/U = Follow-Up

a. Baseline Visit is defined as Day 1, the day of Enrollment and Randomization.

**Table 1. Study Activities (Continued)**

- b. Subjects who prematurely discontinue from the study should complete the procedures outlined for the Discontinuation Visit as soon as possible and preferably prior to the administration of new therapies.
- c. Medical History and Inclusion/Exclusion Criteria must be confirmed by the Investigator prior to enrollment to verify patient eligibility.
- d. Height will be measured at Screening Visit only.
- e. ECG will not be required if the subject had a previous normal ECG within 90 days of Screening, provided all protocol required documentation is available at the site and nothing has changed in the subject's health status since the time of the test that warrants a repeat test. MRI of the SI joint and spine will also not be required if the subject had a previous test within 42 days of Screening, respectively. There is no need to redraw the HLA-B27 or ANA once results are available.
- f. CXR and TB screening will be only performed in subjects in the T2T group for whom initiation of Escalation Step 2 is planned. CRX and TB screening must be performed and evaluated before adalimumab is administered. These procedures will not be required if the subject had a previous normal CXR or negative IGRA within 90 days of the planned start date of adalimumab, provided all protocol required documentation is available at the site and nothing has changed in the subject's health status since the time of the test that warrants a repeat test. If the subject has a positive IGRA test, has had a past CXR consistent with prior TB exposure, the subject will be required to initiate and complete at least the first 1 months of the prescribed TB prophylaxis (Section 5.3.1.1).
- g. All females of childbearing potential will have a serum pregnancy test at Screening.
- h. All females of childbearing potential will have a urine pregnancy test performed at Baseline prior to study enrollment and at study discontinuation/completion. Any subject with a positive urine pregnancy test must have a negative serum test performed prior to enrollment or continuation in the study.
- i. Laboratory assessments (chemistry, hematology, ESR, CRP and urinalysis) will be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.
- j. Dipstick urinalysis will be completed at all required visits. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.
- k. Must be performed and evaluated before adalimumab is administered. If a subject is diagnosed with active hepatitis B (acute or chronic) the subject is not eligible to receive adalimumab and should discontinue from the study.
- l. For subjects that are discontinued prematurely the site should attempt to reschedule the MRI within 2 weeks (14 days) of the Discontinuation Visit or – if this is not possible – shortly thereafter.
- m. SAEs will be collected starting from time of signing informed consent; nonserious AEs will be collected starting from Baseline. Any AE that occurs between Screening and Baseline should be captured as medical history.

**Table 1. Study Activities (Continued)**

- n. Site personnel will contact all subjects of the T2T group who were on treatment with study drug adalimumab during the study but don't continue on commercially available Humira after discontinuation from the study by telephone approximately 70 days after the last dose of study drug to determine the occurrence of AEs or SAEs. Subjects that initiate adalimumab therapy not supplied in the context of the clinical trial after the end of study participation need not be contacted by phone as new AEs or SAEs should be reported through the mechanism used for all post marketing adverse experiences.
- o. ASDASESR will be calculated to determine if treatment escalation is required. The subject will wait in the clinic until the ESR result is available; the ASDASESR results are calculated, and the treatment escalation decision is made.
- p. To be performed if according to the T2T escalation schedule the subject is allocated to study drug.

### **5.3.1.1 Study Procedures**

The study procedures outlined in Table 1 are discussed in detail in this section, with the exception of the collection of AE information (discussed in Section 6.1). All study data will be recorded on the appropriate eCRF pages.

#### **Informed Consent**

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific informed consent will be reviewed, signed and dated by the subject before any study-related procedures are undertaken, or before any medications are withheld from the subject in order to participate in this study.

#### **Inclusion/Exclusion Criteria**

Subjects will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria at both Screening and Baseline Visits.

#### **Medical and Surgical History**

A complete medical and surgical history, including history of tobacco and alcohol use, uveitis, inflammatory bowel disease (CD, UC only), psoriasis, spinal surgery, joint replacement, joint surgery or arthroscopy, will be obtained from each subject during the Screening Visit. An updated medical history will be obtained at the Baseline Visit prior to study treatment administration and updated as necessary throughout the study on the eCRF.

A detailed medical history with respect to TB exposure needs to be documented. This information needs to include Bacillus Calmette-Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations.

An updated medical history will be obtained at the Baseline Visit prior to study treatment administration and updated as necessary throughout the study on the eCRF.

### **Vital Signs/Weight/Height**

Vital signs determinations of systolic and diastolic blood pressure, pulse (counted for at least 30 seconds after 5 minutes in sitting position), respiratory rate, body weight, and body temperature will be obtained at the designated study visits in Table 1. Vital signs should be measured before blood draws are performed and prior to receiving study medication. Height without shoes will be measured at the Screening Visit only.

### **Anterior Uveitis**

At the Screening Visit a detailed medical history of anterior uveitis, as confirmed by an ophthalmologist, will be documented. It should include the date of initial diagnosis, frequency of flares, including specific eye (right, left or both), within the prior 12 months, date of the most recent flare and treatments received in the past.

At Baseline and all subsequent visits, the investigator will document new onset of uveitis and/or the number of flares, including specific eye (right, left or both), since the last visit. The corresponding AE eCRF should also be completed. Initial documentation of uveitis must be confirmed by an ophthalmologist. Flares following initial confirmation by an ophthalmologist can be self-reported by the subject.

### **Physical Examination**

A full physical exam will be performed by medically qualified personnel at the designated study visits in Table 1. Physical examination findings that are related or part of each subject's medical history should be captured on the appropriate eCRF page. The physical exam at the Baseline Visit will serve as the Baseline exam for the entire study.

A symptom-directed physical examination can be performed at any other visits if, in the opinion of the Investigator, it is warranted by the subject's AE status or on review of symptoms. Any clinically significant physical examination findings after the Baseline Visit – or worsening of pre-existing findings – will be recorded as adverse events. For further definition of an adverse event please refer to Section 6.1.1.

### **12-Lead Electrocardiogram (ECG)**

A resting 12-lead ECG will be performed at the Screening Visit. A qualified physician will interpret, determine the clinical significance of any abnormal finding, sign, and date each ECG. Any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. If there is no clinically significant finding this needs to be confirmed in the eCRF. Each signed original ECG will be monitored by the responsible Clinical Research Associate (CRA) and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol required documentation is available and nothing has changed in the subject's health status since the time of the test that warrants a repeat test. If there are other findings that are clinically significant, the Principal Investigator must contact the Study Designated Physician before enrolling the subject.

Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

### **Chest X-Ray (CXR)**

Before initiating T2T Escalation Step 2 (combination with adalimumab) subjects will undergo a standard CXR (Posterior-anterior [PA] and lateral views) to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal chest x-ray within 90 days of the first date of adalimumab administration, provided all protocol required documentation is available at the site (as outlined below in Section 5.3.1.1) and nothing has changed in the subject's health status since the time of the test that warrants a repeat test.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the Investigator.

A radiologist must perform an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the chest x-ray, the Principal Investigator or their physician delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB.

### **Tuberculosis (TB) Screening**

Before initiating T2T Escalation Step 2 (combination with adalimumab) TB screening will be performed. An Interferon-Gamma Release Assay (IGRA; QuantiFERON test or T SPOT TB test) must be performed locally for all subjects who are to escalate T2T treatment to Escalation Step 2 including those with a prior history of BCG administration. If a subject had a negative IGRA test within 90 days prior to the first date of adalimumab administration, and all protocol required documentation is available, this test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

If there are sites where the accepted testing materials are not available an alternative may be substituted, but the method must be submitted to and approved by AbbVie prior to use with study subjects.

A radiologist must perform an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the Principal Investigator or their physician delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator must contact the AbbVie Medical Monitor before enrolling the subject.

If the IGRA test is positive or the subject has a CXR indicative of latent TB, the subject will be required to initiate and complete at least 1 months of the prescribed course of



recommended prophylaxis per German guidelines<sup>44</sup> (Isoniazid 5 mg/kg) prior to starting adalimumab. The visit schedule will continue with the 1<sup>st</sup> dose of study treatment subsequent to completion of TB screening and of at least 1 month of prophylaxis (if applicable).

Subjects with a prior history of latent TB that have a documented completion of the Centers for Disease Control and Prevention (CDC) recommended or local guideline recommended prophylaxis may be permitted to enroll. If the subject has a prior history of latent TB but has not completed or received prophylaxis, prophylaxis must be initiated and the subject must have completed at least 1 months of the prescribed TB prophylaxis before enrolling into the study.

If the subject has a prior history of active TB they must have documentation of completion of CDC recommended or local guideline recommended treatment and documentation of resolution of the infection.

If the IGRA test is indeterminate, the site should repeat the test with another blood sample. If the second IGRA test is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis.

Newly initiated prophylactic treatment should be captured on the concomitant medications page in the eCRF and in the source documents. Prior therapy should be captured in medical history.

For any subject with clinical signs/symptoms of active TB or newly identified TB risk factors a CXR may be required for evaluation of active TB and the site should contact the AbbVie Medical Monitor for further discussion. Subjects with confirmed active TB should be discontinued from the study and receive standard of care treatment for TB.

### **Pregnancy Tests**

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. At the Baseline Visit, subjects of childbearing potential will have

a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed. A lactating or pregnant female will not be eligible for participation or continuation in this study.

All women of childbearing potential will have a repeat urine pregnancy test at the final study visit performed locally by designated study personnel.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

### **Laboratory Analyses**

Blood and urine samples will be obtained for clinical laboratory tests. Samples will be obtained at the designated study visits in Table 1. Samples will be obtained for the laboratory tests listed in Table 2.

The local laboratory of the respective study site will be utilized to process and provide results for the clinical laboratory tests, except for autoantibodies against CD74 CLIP. The local laboratory will provide instructions regarding the collection, processing and shipment of appropriate samples.

The laboratory results will be provided by the local laboratory to the investigative site where they will be reviewed, signed and dated by the Investigator and filed as source data. For any abnormal value outside of the reference range, the Investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

A certified central laboratory will be utilized to process and provide results for the testing of autoantibodies against CD74 CLIP. The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipment of appropriate samples.

The laboratory results will be provided by the central laboratory to the investigative site where they will be reviewed, signed and dated by the Investigator and filed as source data.

Blood draws should be performed after questionnaires and vital sign determinations have been completed but prior to any study treatment administration.

Urine samples will be obtained for macroscopic urinalysis (dipstick done at the local lab). Macroscopic urinalyses will include specific gravity, pH, protein, glucose, ketones, blood and nitrites. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

Clinical laboratory tests will need to be repeated at the Baseline Visit only if the time between the Screening Visit and the Baseline Visit is greater than 14 days.

**Table 2. Clinical Laboratory Tests**

Hematology	Clinical Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Glucose	Specific gravity Ketones pH Protein Glucose Nitrite Blood	Pregnancy test ESR CRP Anti-dsDNA Antibodies HLA-B27 HBsAg HBsAb HBcAb
			<b>Biomarkers</b>
			Autoantibodies against CD74 CLIP

### **Human Leukocyte Antigen-B27 (HLA-B27)**

Testing for HLA-B27 will be performed on specimens collected during the Screening Visit. The HLA-B27 can be used to fulfill the ASAS classification criteria (Appendix C).

For subjects that may need to be rescreened or where the result of a previously documented HLA-B27 test is available, repeat HLA-B27 testing is not required.

### **Anti-dsDNA Antibody**

Testing for antibodies against dsDNA will be performed on specimens collected during the Screening Visit. For subjects that may need to be rescreened, once results are available repeat testing is not required.

### **Hepatitis B Testing**

All subjects will be tested for the presence of the HBV at Screening. A positive result for the HBs Ag will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total = HBc IgG and HBc IgM). Subjects with HBs Ag (-), HBs Ab (-), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing results in (1), (2), or (3) do not require HBV DNA PCR qualitative testing.

- (1) HBc Ab Total (-) and HBs Ab (-): no evidence of prior infection
- (2) HBc Ab Total (-) and HBs Ab (+): immunity due to HBV vaccination
- (3) HBc Ab Total (+) and HBs Ab (+): immunity due to past infection

Subjects with HBs Ag (-), HBs Ab (-), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA to determine if

- Resolved HBV infection
- False positive HBc Ab test
- Low level chronic HBV infection
- Resolving acute HBV infection

Hepatitis B testing (as described above) will be repeated for subjects of the T2T group before initiating escalation step 2. Hepatitis B testing must be performed and evaluated before adalimumab is administered. If a subject is diagnosed with active hepatitis B (acute or chronic) the subject is not eligible to receive adalimumab and should discontinue from the study.

### **C-Reactive Protein (CRP)**

Testing for CRP will be performed on specimens collected at the designated study visits listed in Table 1.

If a subject has an elevated CRP which the investigator believes to be secondary to an AE and not due to axSpA, sites may repeat the CRP later on within the time window allowed for the respective visit following a discussion with the AbbVie Study Designated Physician. Instances where AE-related CRP elevation spans more than one study visit will be addressed on a case-by-case basis.

### **Erythrocyte Sedimentation Rate (ESR)**

Testing for ESR will be performed on specimens collected at the designated study visits listed in Table 1. ESR will be evaluated at the site and expressed in mm/hg (1<sup>st</sup> hour). In order to enable making the decision about T2T treatment escalation at the day of the respective visit,  $ASDAS_{ESR}$  will be calculated for the purpose of decision making.

### **Antibodies Against CD74 CLIP**

Samples will be obtained for biomarker testings at the designated study visits in Table 1.

Sample collection is described in more detail under Section 5.3.2.1. The primary biomarker is anti-CD74 CLIP antibodies.

### **Magnetic Resonance Imaging (MRI) of the Spine and Sacroiliac Joints**

All subjects will have a MRI evaluation of the sacroiliac (SI) joints as well as the cervical, thoracic and lumbar regions of the spine at Screening and the last visit (at Week 52 visit or – in case of early discontinuation – the Discontinuation Visit). All assessments and procedures to determine subject eligibility should be performed and results available, showing subject may be eligible for study participation, before MRI assessment is carried out. The Screening MRI will not be required if the subject had a previous MRI fulfilling the study requirements (actual MRI films must be available to the site) within 42 days of the Screening Visit.

Images will be sent to the central imaging vendor designated by the Sponsor. Images will be scored for inflammatory lesions and chronic structural changes in the spine and the sacroiliac joints using the Berlin MRI score (Appendix S). Information on the central imaging vendor as well as procedures for performing and shipping the MRIs are provided in a separate manual.

### **Tender Joint Count (TJC)**

An assessment of 68 joints will be done by physical examination at the designated study visits in Table 1, by pressure manipulation on physical exam. Joint pain/tenderness will be classified as present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA") (Appendix H).

A joint undergoing surgery or intra-articular injection with corticosteroids will not be evaluable ("NA") for 28 days.

Site should make every attempt to have the same qualified Investigator or designee conduct these assessments throughout the study for any given subject.

### **Swollen Joint Count (SJC)**

An assessment of 66 joints will be done by physical examination at the designated study visits in Table 1. The joints to be examined for swelling are the same as those examined

for tenderness, except the hip joints are excluded. Enthesitis is not part of the swollen joint assessment. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA") (Appendix H).

A joint undergoing surgery or injected intra-articularly with corticosteroids will not be evaluable ("NA") for 28 days.

Site should make every attempt to have the same qualified Investigator or designee conduct these assessments throughout the study for any given subject.

#### **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)**

The BASDAI will be completed at the designated study visits in Table 1. The subject will assess his/her disease activity using the BASDAI which consists of Numerical Rating Scale (NRS) used to answer 6 questions pertaining to symptoms experienced by the subject during the past week (Appendix F).

#### **Linear Bath Ankylosing Spondylitis Metrology Index (BASMI<sub>lin</sub>)**

The BASMI<sub>lin</sub> will be conducted at the designated study visits in Table 1 to evaluate spinal mobility in a subject (Appendix I).

Site should make every attempt to have the same qualified Investigator or designee conduct these assessments throughout the study for any given subject.

#### **Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)**

The MASES evaluation will be conducted at the designated study visits in Table 1 to assess the presence or absence of enthesitis at 13 different sites, noting the subjects' responses (Appendix J).

Site should make every attempt to have the same qualified Investigator or designee conduct these assessments throughout the study for any given subject.

### **Dactylitis**

Evaluation for dactylitis will be conducted at the designated study visits in Table 1 to assess the presence or absence of dactylitis in all 20 of the subjects' digits.

Site should make every attempt to have the same qualified Investigator or designee conduct these assessments throughout the study for any given subject.

### **Bath Ankylosing Spondylitis Functional Index (BASFI)**

The BASFI will be completed at the designated study visits in Table 1. The subject will assess his/her ability of ten selected activities for the past week using a NRS (Appendix K). This assessment should be completed prior to any other study related procedures being performed.

### **Numerical Rating Scales (NRS)**

NRS will be used to assess physician's and patient's global assessment of disease activity, as well as the patient's global assessment of pain, patient's assessment of nocturnal back pain, and patient's assessment of total back pain. The left end of the NRS (0) signifies the absence of symptoms and the right end (10) signifies maximum activity in terms of the parameters assessed:

- Physician's global assessment of disease activity (current status)
  - Physician's global assessment of patient's current disease activity (Appendix L). Site should make every attempt to have the same qualified Investigator or designee (physician required) conduct these assessments throughout the study for any given subject.
- Patients global Assessment of Disease activity within the last week (Appendix G)
- Patient's assessment of nocturnal back pain within the last week (Appendix M)
- Patient's assessment of total back pain within the last week (Appendix N)
- Patient's global assessment of pain within the last week (Appendix O)



### **Health Outcomes Questionnaires**

Subjects will complete the following questionnaires: ASAS Health Index (HI) (Appendix P), European Quality of Life – 5 Dimension Questionnaire (EQ-5D) (Appendix R), and Work Productivity and Activity Impairment Questionnaire – Specific Health Problem Questionnaire (WPAI-axSpA) (Appendix Q). The ASAS HI will assess the overall functioning of each subject. The EQ-5D will assess the subject's view of their health. The WPAI-axSpA will assess work related issues. These assessments should be completed prior to any other study related procedures being performed in the order outlined on Table 1.

### **Prior and Concomitant Therapy Assessment**

Any medication that the subject is receiving at the time of Screening or receives during the study must be recorded on the source documents as well as the appropriate eCRF. Previous prescription medications or physician-administered treatments used for axSpA prior to study entry will be recorded. See Section 5.2.3 for full details regarding documentation of prior and concomitant therapy.

### **Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation (Treat-to-Target [T2T] Group)**

The ASDAS<sub>ESR</sub> will be calculated for each visit as outlined in Table 1 for subjects in the T2T group. The ASDAS<sub>ESR</sub> will be calculated using the parameters listed in Appendix E of the respective visit including the ESR measurement of the respective visit.

The ASDAS<sub>ESR</sub> will be automatically calculated by the eCRF upon entry of the respective parameters.

In order to enable making the decision about T2T treatment escalation on the day of the respective visit, ASDAS<sub>ESR</sub> will be calculated. The subject will need to wait at the site for approximately 1 hour until the ESR result is available, the ASDAS<sub>ESR</sub> is calculated, and treatment escalation decision is made.

Published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease";  $\geq 1.3$  to < 2.1 for "moderate disease activity";  $\geq 2.1$  to  $\leq 3.5$  for "high disease activity" and > 3.5 for "very high disease activity."<sup>33</sup>

If a subject has an elevated ESR which the investigator believes to be secondary to an AE and not due to axSpA, sites may repeat the ESR later on within the time window allowed for the respective visit following a discussion with the AbbVie Study Designated Physician. Instances where AE-related ESR elevation spans more than one study visit will be addressed on a case-by-case basis.

### **Enrollment and Randomization**

Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will be enrolled into the Randomized Open-Label Treatment Period randomized in a 1:1 ratio to receive either T2T treatment or SOC as outlined in Section 5.1. Subjects will not be enrolled in the study if laboratory or other screening results are clinically unacceptable.

As they are enrolled into the study, subjects will be assigned unique consecutive numbers starting with 10001\_\_, whereas, the first 2 digits represent the country, the next 3 digits represent the site number and the last 2 digits represent a sequential number. Site numbers will be assigned sequentially.

### **Dispense Study Drug**

Study drug will be dispensed to subjects as outlined in Table 1 and described in more detail under Section 5.5.

### **Administration of Study Drug**

The first time study drug is administered this will be done under direct observation in the Investigator's office to ensure proper technique as described in more detail under Section 5.5.

### **70-Day Follow-Up Call for Treat-to-Target (T2T) Group**

Subjects of the T2T group who were on treatment with study drug adalimumab during the study but do not continue on commercially available Humira after completing or discontinuation from the study will be contacted approximately 70 days following their last dose of study drug to check for new, and update ongoing AEs or Serious AEs (SAEs) except those subjects that continue on Humira therapy after the end of study participation. Any new AEs/SAEs reported during the 70-day follow-up period should be submitted to AbbVie. The 70-day follow-up phone call will be recorded in source document only and confirmation of the contact will be faxed to AbbVie (Appendix T). Subjects that continue on adalimumab therapy after study end are not required to complete the 70-day follow-up and any new AEs should be reported through the mechanism used for all post marketing adverse experiences.

## **5.3.2 Measurement of Autoantibodies Against CD74 CLIP**

### **5.3.2.1 Collection of Samples for Analysis**

Please refer to the central laboratory manual for specific instructions regarding sample collection, processing, storage and shipment.

Blood samples for the detection of autoantibodies against CD74 CLIP will be obtained, when the blood samples are drawn according to the local standards at each center at Baseline, Week 32, 52, and at discontinuation visit in the case of early discontinuation per Section 5.3.2. The serum sample (2 mL) for the central laboratory in Hannover, Germany, will be obtained and processed as described below.

The date that each blood sample is collected will be recorded in the appropriate eCRF.

Sample collection will be **prior to dosing of adalimumab** (if appropriate) at the study visits specified in Table 1.

---

### **5.3.2.2 Handling/Processing of Samples for the Detection of Autoantibodies Against CD74 CLIP**

Within 2 hours after the blood sample was obtained, the tube will be spun down (see laboratory manual for detailed instructions). The supernatant will be frozen immediately and stored at at least  $-20^{\circ}\text{C}$ . The serum samples will be pseudonymized using the subject's unique identification code and initially stored at the site where the subject was recruited.

### **5.3.2.3 Disposition of Samples for the Detection of Autoantibodies Against CD74 CLIP**

Shipment of pseudonymized samples to the central laboratory will be done by a courier service on dry ice per the central laboratory instruction manual when 20 sera have been collected or every 3 months, whatever is earlier. An inventory of the samples included will accompany the package.

The shipment address for the samples is:



The samples will be stored in the central lab at at least  $-70^{\circ}\text{C}$  until they are used for the study specific analysis of the antibodies against CD74 CLIP. Remaining rest of serum samples will be discarded.

### **5.3.3 Efficacy Endpoints**

#### **5.3.3.1 Primary Efficacy Endpoint**

The primary efficacy endpoint is the clinical disease activity at Week 32 as measured by the percentage of subjects in ASDAS inactive disease (ASDAS < 1.3).

#### **5.3.3.2 Secondary Endpoints**

Secondary endpoints include the following:

At Week 32 and Week 52

- Quality of life by the EQ-5D Questionnaire
- WPAI-axSpA
- Overall functioning by ASAS HI
- Disease activity as measured by BASDAI
- Percentage of subjects achieving 50% improvement in BASDAI (BASDAI 50 response)
- Function – Represented by the BASFI NRS score (0 to 10)
- Disease activity measured by ASDAS
- ASDAS major improvement
- 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)
- 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 (PTGA) – 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  $\geq 3$  of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain
  - ASAS partial remission: absolute score of  $< 2$  units for each of the 4 domains identified above in ASAS20
  - Active inflammation as measured by magnetic resonance imaging of the sacroiliac joints and the spine (Berlin MRI scores for MRI of the SI joint and spine)
  - Physician's Global Assessment of Disease Activity
  - Patient's Global Assessment of Disease Activity
  - Patient's Global Assessment of Pain
  - Swollen Joint Count (66 joints)
  - Tender Joint Count (68 joints)
  - Change from Baseline in MASES
  - Change from Baseline in Dactylitis count (0 – 20)
  - Change from Baseline in BASMI<sub>lin</sub>
  - Anterior uveitis

Other variables to be analyzed at various time points including Week 32 and Week 52 include:

- C-reactive Protein
- Erythrocyte sedimentation rate

- ASDAS course over time
- BASDAI course over time

#### **5.3.3.3 Exploratory Endpoints**

- Serum autoantibodies against CD74 CLIP
- Reduction of disease progression (as measured by MRI of the sacroiliac joints and the spine)

#### **5.3.4 Safety Variables**

Screening assessments will include medical history, vital signs, physical examination, and clinical laboratory tests. The following safety evaluations will be performed during the study: medical history and concomitant medication review, AE monitoring, assessments of vital signs, physical examination and laboratory tests.

### **5.4 Removal of Subjects from Therapy or Assessment**

#### **5.4.1 Discontinuation of Individual Subjects**

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation prematurely for any reason, including an adverse event, safety concerns or failure to comply with the protocol. See section 6.1.7 for toxicity management criteria.

Subjects will be withdrawn from the study immediately if any of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Study Designated Physician.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noticed after the subject started study drug, when continuation of the study drug would place the subject at risk

as determined by the AbbVie Study Designated Physician (Section 5.2 and Section 7.0).

- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Study Designated Physician.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study.
- Subject has dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie Study Designated Physician.

If, during the course of the study, the subject prematurely discontinues from the study, the procedures outlined for the Discontinuation Visit must be completed within 2 weeks of the last dose of study drug (if applicable), and, if possible, prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final phone call will be made to subjects of the T2T group who were on treatment with study drug adalimumab during the study but do not continue on commercially available Humira after discontinuation from the study approximately 70 days after the end of their Treatment phase (i.e., their Week 52 visit) or – in case of premature discontinuation – their Discontinuation Visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs unless not required as outlined in Section 5.3.1.1.



All attempts must be made to determine the date of the last dose of study drug and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. As a minimum, two phone calls must be made and one certified letter must be sent. The attempts should be documented in the subject's source documents.

#### **5.4.2 Discontinuation of Entire Study**

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. AbbVie will terminate the trial prematurely if any new safety signal for the study drug is identified which indicates an unacceptable risk for patients in this trial. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

### **5.5 Treatments**

#### **5.5.1 Treatments Administered**

##### T2T Group

Treatment escalation steps are as follows:

- Basic Treatment (NSAID 1): Treatment will be started with any NSAID at full anti-inflammatory dose and given for 4 weeks (see Appendix Y). Early escape is possible, if after 2 weeks no ASAS 20 response is achieved. In this case, treatment can be switched to Escalation Step 1 at the Week 2 visit. If the chosen NSAID cannot be continued due to intolerance, escalation to the next

escalation step is possible at any time point. If Basic Treatment is well tolerated and ASDAS is  $< 2.1$  the subject will be continued on this treatment.

- Escalation Step 1 (NSAID 2): At Week 4 (after 4 weeks of NSAID 1), if ASDAS is  $\geq 2.1$  or treatment with NSAID 1 is not tolerated, treatment will be changed to a second NSAID at full anti-inflammatory dose (see Appendix Y). The second NSAID will be given for 4 weeks. Early escape is possible if after 2 weeks (at Week 6 or Week 4 for subjects who early escaped from Basic Treatment) no ASAS 20 response is achieved. In this case, treatment can be switched to Escalation Step 2 after 2 weeks of NSAID 2. If the chosen NSAID cannot be continued due to intolerance, escalation to the next escalation step is possible at any time point. In that case, adalimumab may be combined the second or – if deemed required by the treating physician – the first NSAID used (provided escalation from Basic Treatment to Escalation Step 1 did not occur due to any safety issues related to NSAID 1 therapy). If NSAID 2 treatment is well tolerated and ASDAS is  $< 2.1$ , the subject will be continued on this treatment.
- Escalation step 2 (Combination with adalimumab): In case of failure of NSAID 2 (ASDAS  $\geq 2.1$  after 4 weeks of NSAID 2) the treatment will be intensified by switching to the combination of NSAID and adalimumab 40 mg s.c. eow. Escalation step 2 can be initiated at Week 4 visit at the earliest if early escape is chosen during basic treatment and during NSAID 2.

Since subjects may be unfamiliar with sterile SC injection technique, qualified study site personnel will instruct them on proper technique and should directly observe the first injection of study drug to ensure proper injection technique (Appendix U). This supervision will serve as a confirmation of the use of safe and appropriate drug injection techniques and to answer any questions related to drug administration.

#### SOC Group

Subjects will receive treatment according to local SOC. For use of NSAID please see Appendix Y.

## 5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3.

**Table 3. Identity of Investigational Products**

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Pre-filled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie

### 5.5.2.1 Packaging and Labeling

Investigational product (IP) will be packaged separately in 0.8 mL syringes containing adalimumab 40 mg/0.8 mL. Each dosing kit carton will contain two pre-filled syringes to accommodate study design.

The syringe and/or carton labels will minimally contain the information as required per country requirements.

All labels must remain affixed to study medication at all times, and should never be removed for any reason.

### 5.5.2.2 Storage and Disposition of Study Drug

Adalimumab pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study medication drug **must not be frozen** at any time. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded on each business day. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study medication should be quarantined and not dispensed until AbbVie Global Pharmaceutical Research and Development (GPRD) or

AbbVie Temperature Excursion Management System (ATEMS) deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are destroyed via on-site destruction (if allowed by AbbVie, local guidelines and a well-documented procedure is in place) or returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study.

### **5.5.3 Method of Assigning Subjects to Treatment Groups**

All subjects will be enrolled at the Baseline Visit and centrally randomized in a 1:1 ratio to the two treatment arms (intensified T2T or SOC). Centralized permuted block randomization will be performed.

### **5.5.4 Selection and Timing of Dose for Each Subject**

Subjects should take study medication as outlined in Section 5.5.1.

If a subject should in the T2T group forget to administer the injection of study medication on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all dosing information on the Subject-Dosing Diary Sheet (Appendix V).

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. Remaining doses should be fully returned to the study site. The subject should resume their regular dosing schedule based on the first dosing date at Baseline.

## **5.5.5 Blinding**

### **5.5.5.1 Blinding of Investigational Product**

Neither the investigator(s) nor their study staff, or subjects will be blind to the treatment arm subjects are randomized to. The investigator should not influence their SOC treatment based upon knowledge and potential benefits/risks in the intensified T2T treatment arm.

## **5.5.6 Treatment Compliance**

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study.

The subject or their qualified designee will administer all doses of study drug. Appropriate site staff will supervise the first administration of the study drug in-office to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a subject dosing diary sheet (Appendix V) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. Subjects will be instructed to return all drug containers (even if empty) to the study site. If the subject does not return the subject dosing diary sheet, IP boxes and sharp containers (when applicable), the site should question the subject and obtain as much information as possible as to the dosing of the study drug. The information should be documented on the source documents as per "best recollection" and when possible re-verified once the dosing sheet is returned before completing the applicable eCRF page.

## **5.5.7 Drug Accountability**

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature, and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar

document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the site on a Site Drug Accountability log including date received, the lot number, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug.

All empty IP boxes and used pre-filled syringes will be inventoried by the site. Each subject will be given their own sharps disposal container to store used pre-filled syringes. Empty IP boxes and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty Boxes and returned Sharps containers will be retained (unless prohibited by local law) until the CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via study medication logs, source documents, subject dosing sheets, empty IP boxes and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff may destroy or initiate shipment for shipment of used pre-filled syringes. Site staff and CRA will document that the used pre-filled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the destruction methodology should be maintained at the site's facility. At the end of the study, after drug accountability has been completed at the site and verified by the CRA, unused medication will be returned to a destruction facility by the CRA or – if approved by AbbVie and permitted according to local guidelines – destroyed at site (or by a third party vendor contracted by the site).

## **5.6 Discussion and Justification of Study Design**

### **5.6.1 Discussion of Study Design and Choice of Control Groups**

This clinical trial was designed to compare a T2T intensified treatment approach (escalating quickly with two different NSAIDs to a combination of adalimumab with NSAID) with SOC in reducing disease activity/achieving remission in patients with

axSpA. Recently T2T recommendations for the whole group of SpA including patients with axSpA have been developed. However, a T2T approach starting with NSAID treatment and escalating to combining NSAID with a TNF blocker has not yet been investigated.

The duration of 52 weeks was chosen to reasonably reflect long term treatment of chronic disease.

### **5.6.2 Appropriateness of Measurements**

Standard statistical, clinical and laboratory procedures will be utilized in this study. Efficacy measurements in this study have been selected to assess disease activity in subjects with axSpA. Other than the biomarker analysis and the measurement of MRI progression which will be exploratory, all clinical and laboratory procedures in this study are standard and generally accepted.

### **5.6.3 Suitability of Subject Population**

Males and females at least 18 years of age with axSpA who have a minimum level of disease activity at Baseline (ASDAS  $\geq 2.1$ ). Confining the duration of disease to  $< 5$  years and including only subjects who are TNF-alpha-blocker-naïve and either NSAIDs-naïve or should not have taken NSAIDs at maximal recommended dose over the last 2 weeks prior to Baseline minimizes the probability to include treatment experienced/resistant subjects.

### **5.6.4 Selection of Doses in the Study**

The recommended dose of adalimumab for adults with AS and nr-axSpA is 40 mg administered eow. Adalimumab is approved for the treatment of AS and nr-axSpA in the EU. Adalimumab was generally well-tolerated and has demonstrated therapeutic efficacy compared to placebo in AS subjects in Study M03-607 (ATLAS) and Study M03-606 as well as in nr-axSpA subjects in Study M10-791 which were the pivotal studies used to support registration for these indications.

## **6.0 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

The study medication in this trial contains both:

A Biologic compound and

Device components (pre-filled syringe)

Complaints associated with any component of this study medication must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.6. For product complaints, please refer to Section 6.2.

### **6.1 Medical Complaints**

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to Humira, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with Humira, the Investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.



## **6.1.1 Definition**

### **6.1.1.1 Adverse Event**

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this 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 (investigational) 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 protocol or 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.

Worsening of SpA per investigator judgment is considered an AE, however the expected manifestations of disease (arthritis, enthesitis, back pain, etc.) are not considered AEs.

Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section 6.1.7 regarding toxicity management]) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

### 6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

<b>Death of Subject</b>	An event that results in the death of a subject.
<b>Life-Threatening</b>	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.
<b>Hospitalization or Prolongation of Hospitalization</b>	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
<b>Congenital Anomaly</b>	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
<b>Persistent or Significant Disability/Incapacity</b>	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. 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).
<b>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome</b>	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 subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

### 6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

<b>Mild</b>	The adverse event is transient and easily tolerated by the subject.
<b>Moderate</b>	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
<b>Severe</b>	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

### 6.1.3 Relationship to Humira

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of Humira:

<b>Reasonable Possibility</b>	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is <b>sufficient</b> evidence (information) to suggest a causal relationship.
<b>No Reasonable Possibility</b>	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is <b>insufficient</b> evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to Humira will be considered "associated." Events assessed as having no reasonable possibility of being related to Humira will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

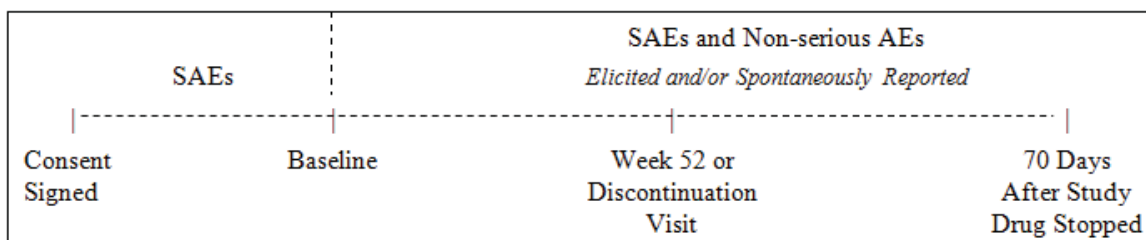
If an Investigator's opinion of no reasonable possibility of being related to Humira is given, an "Other" cause of event must be provided by the Investigator for the adverse event.

#### 6.1.4 Adverse Event Collection Period

All adverse events reported from Baseline until 70 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent. Adverse event information will be collected and recorded on the appropriate eCRFs.

Subjects who continue on Humira therapy eow after the end of study participation will not be contacted for follow-up as any new adverse events should be reported through the mechanism used for all post-marketing adverse experiences. All other subjects of the T2T group treated with study drug will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs. The 70-day follow-up call will not be required for subjects of the SOC group. The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later. All SAEs and all ongoing adverse events reported during the 70-day follow-up phone call must be captured in the clinical database.

**Figure 2. Adverse Event Collection**



### 6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to Humira or not, the physician will notify the AbbVie Clinical Pharmacovigilance Team within 24 hours of the site being made aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the EDC system or if the EDC system is not operable should be documented on the SAE Non-CRF Forms and sent (preferable by email) to Clinical Pharmacovigilance within 24 hours of being made aware of the adverse event.



For safety concerns, contact:



For any subject safety concerns, please contact the physician listed below:

Primary Study Designated Physician:



Should in case of subject safety concerns or medical emergencies the Study Designated Physician be unavailable, please call the following central back-up number

<b>Phone:</b> 
---

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

#### **6.1.6 Pregnancy**

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be prematurely discontinued (Section 5.4.1). Pregnancies will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome for either mother or infant, meeting any serious criteria including elective or spontaneous abortion is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

---

### 6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (see Section 6.1 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

**Management of Select Laboratory Abnormalities:** For any given confirmed laboratory abnormality (repeat testing with a new sample), the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values (confirmation by repeat testing is required) are described in Table 4.

**Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values**

Laboratory Parameter	Toxicity Management Guideline
Absolute neutrophil count (ANC)	<ul style="list-style-type: none"> <li>Discontinue from study if confirmed <math>&lt; 500</math> cells/<math>\mu</math>L by repeat testing with new sample.</li> </ul>
Absolute lymphocyte counts (ALC)	<ul style="list-style-type: none"> <li>Discontinue from study if confirmed <math>&lt; 500</math> cells/<math>\mu</math>L by repeat testing with new sample.</li> </ul>
Total white blood cell count	<ul style="list-style-type: none"> <li>Discontinue from study if confirmed <math>&lt; 1000</math> cells/<math>\mu</math>L by repeat testing with new sample.</li> </ul>
Platelet count	<ul style="list-style-type: none"> <li>Discontinue from study if confirmed <math>&lt; 20,000</math> cells/<math>\mu</math>L by repeat testing with new sample</li> </ul>
AST or ALT	<ul style="list-style-type: none"> <li>Discontinue from study if confirmed ALT or AST <math>&gt; 3 \times</math> ULN and total bilirubin <math>&gt; 2 \times</math> ULN (repeat testing with new samples are required for both)</li> <li>Discontinue from study if confirmed ALT or AST <math>&gt; 3 \times</math> ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (<math>&gt; 5\%</math>).</li> <li>Discontinue from study if confirmed ALT or AST <math>&gt; 8 \times</math> ULN by repeat testing with new sample.</li> </ul>
Serum Creatinine	Discontinue study drug if confirmed $> 3 \times$ ULN by repeat testing with new sample.

## 6.2 Product Complaint

### 6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device components. 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 subject 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.

### **6.2.2 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 the Product Complaint form. 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 may require return of the product with the alleged complaint condition (syringe). 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.

## **7.0 Protocol Deviations**

AbbVie does not allow intentional/prospective deviations from the protocol. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable), and their assigned CRO Clinical Monitor or the following AbbVie Clinical Monitors:

Primary Contact:

Alternate Contact: (CPM)

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

For the purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though she/he did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

## **8.0 Statistical Methods and Determination of Sample Size**

### **8.1 Statistical and Analytical Plans**

#### **8.1.1 Analysis Population**

The primary and secondary efficacy variables will be analyzed for the intent to treat (ITT) population, defined as all subjects who were randomized to one of the two treatment arms. Subjects in the ITT population will be analyzed according to the treatment group they were randomized to. In order to evaluate the impact of major protocol violations on the results of the trial, additional analyses of the primary efficacy variable may be conducted on the per-protocol population, which consists of all ITT subjects who were randomized,

have sufficient data regarding the primary efficacy endpoint (clinical disease activity at Week 32) and did not meet any major protocol violation.

The safety population consists of all subjects who were randomized and received treatment for axSpA after randomization.

### **8.1.2 Statistical and Analytical Plan**

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. The analysis will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

Unless otherwise stated, all statistical tests will be conducted at  $\alpha = 0.05$  level (2 sided). Descriptive statistics data will be provided including but not limited to the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables; and counts and percentages for discrete variables.

All statistical comparisons for the primary efficacy endpoint will be performed at Week 32 and secondary efficacy endpoints will be performed at the time points specified in Section 5.3.3.2, unless otherwise stated. All statistical comparisons for the primary and secondary endpoints will be done at the end of the study.

The last available pre-treatment values recorded on or before Day 1 will be considered as the Baseline value.

In case of missing data for the primary efficacy endpoint (proportion of subjects with ASDAS < 1.3 at Week 32), the non-responder imputation (NRI) will be applied, i.e., missing value at Week 32 will be counted as non-response.

In addition to this imputation approach, the following sensitivity analyses will be performed:

1. Observed cases: all subjects with data available at Week 32 will be analyzed without imputation.
2. Last observation carried forward (LOCF) rule: replacing the missing value by the last non-missing post-baseline value prior to the missing value.

The LOCF rule will be also applied to impute missing continuous efficacy data at post-Baseline Visits (including Week 52). In addition, an analysis using only the observed or reported data will be performed as a sensitivity analysis for the continuous secondary efficacy endpoints.

### **8.1.3 Analysis of Demographic Data and Baseline Disease Characteristics**

Demographic and Baseline characteristics will be summarized and compared, among treatment groups. The number of observations, mean, standard deviation, median, quartiles, minimum and maximum will be summarized for continuous variables; and treatment group homogeneity will be assessed using a one-way analysis of variance (ANOVA) model using treatment, as the independent factor. Discrete variables will be summarized via counts and percentages; and treatment group homogeneity will be evaluated using the appropriate chi-square method. Duration of treatment will be summarized. Medical History will be presented by count and percentage of subjects broken down by Body System and Diagnosis.

### **8.1.4 Statistical Analysis of Efficacy**

#### **8.1.4.1 Analysis of Primary Efficacy Endpoint**

The primary efficacy endpoint is the response rate of clinical disease activity at Week 32 as measured by the percentage of subjects with ASDAS inactive disease ( $ASDAS < 1.3$ ) in the two treatment arms.

The null hypothesis states that there is no difference in response rates between the intensified T2T arm and the SOC arm; the alternative hypothesis is that the response rates

are different. The response rates will be tested using a two-sided Pearson's chi-square test with  $\alpha = 0.05$ . The Fisher's exact test will be applied, if  $\geq 25\%$  of the cells in the frequency table have expected counts less than 5.

For subjects with missing data at Week 32 regarding the primary endpoint the imputation rules specified in Section 8.1.2 will be applied.

The ITT analysis will be considered as primary analysis.

#### **8.1.4.2 Analysis of Secondary Efficacy Endpoints**

The null hypothesis for each secondary efficacy endpoint is that there is no difference between the intensified T2T arm and the SOC arm in the ITT analysis; the alternative hypothesis is that there are differences between the two treatment arms. All statistical tests which will be performed for secondary endpoints are only of exploratory nature and no adjustment for multiple comparisons is planned.

Discrete variables will be summarized using count and percentages will be compared between the two treatment arms using Pearson's chi-square. The Fisher's exact test will be applied instead of the chi-square test, if  $\geq 25\%$  of the cells in the frequency table have expected counts less than 5.

Continuous efficacy variables will be summarized by common statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum and maximum) at Baseline, post-baseline Time points and for change from Baseline to the post-baseline Time points. The changes from Baseline to Week 52 in continuous variables will be compared between the treatment arms using an analysis of covariance method adjusting for the corresponding Baseline values and treatment arm as independent factor. Least square mean values (LSMEAN) for the difference of the mean changes between the two treatment arms and corresponding 95% confidence intervals will be determined. This will be done both for the observed and LOCF imputed values. All further details will be specified in the SAP.

---

#### **8.1.4.3 Other Exploratory Analyses**

Other exploratory analyses will be specified in the SAP.

#### **8.1.5 Pharmacokinetic Analyses**

No pharmacokinetic investigations are planned.

#### **8.1.6 Safety Analysis**

Safety analyses will be carried out using the safety population, which include all subjects who were randomized and received treatment for axSpA after randomization.

Treatment-emergent AEs and serious AEs (SAEs), which include pre- and post-treatment SAEs, will be summarized and reported, while pre-randomization AEs will be only listed.

Treatment-emergent AEs are defined as AEs that begin either on or after the Baseline Visit up to end of the study. All AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®). The number and percent of subjects experiencing treatment emergent AEs will be tabulated by system organ class and preferred term. In addition, a summary of treatment emergent AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, and those which lead to premature study discontinuation will be listed and described in detail.

Mean change in vital signs and laboratory variables at each visit as compared to Baseline will be summarized for all subjects in the safety population, and compared between treatment groups using a one way ANOVA. The last evaluation on or before the Baseline Visit will be used as baseline for all analyses. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 3 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variables.

#### **8.1.7 Interim Analysis**

No interim analysis is planned for this study.

## 8.2 Determination of Sample Size

In the relevant RA strategy trials the drop-out rates were 3.6% after 2 years in the STREAM study,<sup>44</sup> 6.4% after 18 months in the TICORA study<sup>15</sup> and 32.1% after 2 years in the CAMERA trial.<sup>14</sup>

In the RA T2T trials remission was reached in 50% (tight control) versus 37% (usual care) in the CAMERA trial (DMARD trial) after 2 years,<sup>14</sup> in 31% versus 18% after 1 year in another trial,<sup>17</sup> in 65% versus 16% in the TICORA trial after 18 months of follow-up<sup>15</sup> and in 55% (tight control) versus 30% (usual care) after 1 year (including the possibility to use TNF-blockers).<sup>16</sup>

In a recently performed trial (INFAST) 51.4% of patients with early axSpA who had a disease duration of < 3 years and who were not yet NSAID failures reached a status of ASDAS inactive disease during combination treatment with a TNF-blocker and an NSAID compared to 19.6% of patients who reached ASDAS inactive disease during NSAID treatment.<sup>9</sup> This treatment in the INFAST trial comes closest to the T2T arm in the study proposed here.

Data from the NOR-DMARD register, which is a Norwegian longitudinal observational study, including 212 patients with mean disease duration of 9.9 years, showed that ASDAS inactive disease was reached by 33.6% of patients after 3 months of treatment with a TNF-blocker in routine care.<sup>40</sup>

In the observational GESPIC cohort (Year 6) only 12.3% of patients with potentially full access to TNF-blocker therapy reached a status of ASDAS inactive disease.

Based on the above discussed available data it is assumed that ASDAS inactive disease could be reached by 40% in the T2T group versus 20% in the control group. In total  $2 \times 90$  evaluable patients are necessary to detect with 80% power an increase in ASDAS inactive disease at Week 32 from 20% in the SOC arm to 40% in the intensified T2T arm, if a two sided Fisher's exact test is applied. If the Pearson chi-square test instead of the

Fisher's exact test can be applied (see Section 8.1.4.1), then only  $2 \times 83$  patients are necessary.

Assuming that about 18% of the randomized subjects will drop out prior to Week 32 and has to be counted as non-responder the assumed ASDAS inactive disease rate will be diluted to 16.4% in the SOC arm and 32.8% in the intensified T2T arm. The necessary sample size for this scenario (ITT population) is  $2 \times 109$  subjects for the chi-square test and  $2 \times 119$  subjects for the Fisher's exact test. In summary,  $2 \times 120$  subjects should be randomized.

### **8.3 Randomization Methods**

Subjects who meet the eligibility criteria (see Section 5.2) will be randomized in a 1:1 ratio to the two treatment arms (intensified T2T or SOC). Centralized permuted block randomization will be performed.

## **9.0 Ethics**

### **9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)**

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The Investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP and all other applicable regulatory requirements.



Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

## **9.2 Ethical Conduct of the Study**

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical Investigator are specified in Appendix A.

## **9.3 Subject Information and Consent**

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

## **10.0 Source Documents and Case Report Form Completion**

### **10.1 Source Documents**

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The following assessments that will be completed by the subject or physician may be considered source documentation:

BASDAI

BASMI<sub>lin</sub>

BASFI

MASES

Physician's Global Assessment of Disease Activity NRS

Patient's Global Assessment of Disease Activity NRS

Patient's Assessment of Nocturnal Back Pain NRS

Patient's Assessment of Disease Severity

Patient's Global Assessment of Disease Severity NRS

Patient's Global Assessment of Pain NRS

ASAS HI

EQ-5D

WPAI-axSpA

subject Dosing Diary Sheet

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

## 10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system provided by the technology vendor Amedon GmbH, Willy-Brandt-Allee 31 c, 23554 Lübeck, Germany. The documentation related to the validation of the EDC system and study-specific eCRFs is available through the vendor, Amedon, and will be archived as required.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary 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. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Patient Reported Outcomes (PRO) data are collected directly onto paper source worksheets by the subjects. The completion of these forms is verified by the site staff. The source worksheets will be entered into the EDC system by the site staff.

Amedon will provide access to the EDC system for the duration of the trial 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 (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

## **11.0 Data Quality Assurance**

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

An Investigator's Meeting will be held with AbbVie personnel, the investigators and their study coordinators and the Monitors for the study. This meeting will include a detailed discussion of the scientific rationale, protocol, performance of study procedures, eCRF and Subject Diary and log completion, Imaging requirement, and specimen collection methods. In addition to or instead of the Investigator's Meeting, the study personnel at each site may be trained on the study procedures by a Monitor at a study initiation visit and will be given an eCRF completion guideline for reference.

The CRO Monitors will monitor each site throughout the study. Source document review will be performed against entries in the eCRF database and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations.

All central laboratory results will be electronically transferred from the central laboratory to the study database.

A review of the data will be conducted by a physician and clinical review team at AbbVie as specified in the safety review plan.

## **12.0 Use of Information**

Please refer to the Investigator site contract for specific information related to publication practices.

AbbVie abides by the PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial results. AbbVie's registrations and results disclosure adhere to all relevant state and federal laws.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

### **13.0 Completion of the Study**

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator and AbbVie.

The Investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

## 14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: STRIKE – Treating Patients with Early Axial Spondyloarthritis to Target – a 1 Year Randomized Controlled Study Taking an Intense Treatment Approach Versus Routine Treatment

Protocol Date: 30 March 2017



26-APR-2017

Date

Name of Principal Investigator (printed or typed)

## 15.0 Reference List

1. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis.* 2009;68(6):777-83.
2. Sieper J, van der Heijde D. Review: nonradiographic axial spondyloarthritis: new definition of an old disease? *Arthritis Rheum.* 2013;65(3):543-51.
3. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis.* 2011;70(6):896-904.
4. Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69(4):631-7.
5. Smolen JS, Braun J, Dougados M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis.* 2014;73(1):6-16.
6. Song IH, Poddubnyy DA, Rudwaleit M, et al. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. *Arthritis Rheum.* 2008;58(4):929-38.
7. Poddubnyy D, Rudwaleit M, Haibel H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. *Ann Rheum Dis.* 2012;71(10):1616-22.
8. Kroon F, Landewe R, Dougados M, et al. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2012;71(10):1623-9.

9. Sieper J, Lenaerts J, Wollenhaupt J, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, part 1. *Ann Rheum Dis.* 2014;73(1):101-7.
10. Dougados M, Paternotte S, Braun J, et al. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis.* 2011;70:249-51.
11. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum.* 2008;58(7):1981-91.
12. Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum.* 2009;60(4):946-54.
13. Song IH, Hermann K, Haibel H, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis.* 2011;70(4):590-6.
14. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis.* 2007;66(11):1443-9.
15. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet.* 2004;364(9430):263-9.
16. Schipper LG, Vermeer M, Kuper HH, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis.* 2012;71(6):845-50.



17. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. *Ann Rheum Dis*. 2010;69(1):65-9.
18. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*. 2005;52(11):3381-90.
19. Coates LC, Moverley AR, McParland L, et al. Results of a randomised controlled trial comparing tight control of early psoriatic arthritis (TICOPA) with standard care: tight control improves outcome. *Arthritis Rheum*. 2013;65(10): S346.
20. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet*. 2015;386(10012):2489-98.
21. van der Heijde D, Sieper J, Maksymowych WP, et al. Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(6):905-8.
22. Rudwaleit M, Listing J, Brandt J, et al. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann Rheum Dis*. 2004;63(6):665-70.
23. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis*. 2013;72(6):815-22.
24. Rudwaleit M, Claudepierre P, Wordsworth P, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol*. 2009;36(4):801-8.
25. Poddubnyy D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann Rheum Dis*. 2011;70(8):1369-74.

26. Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis Rheum.* 2012;64(5):1388-98.
27. Lukas C, Landewe R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2009;68(1):18-24.
28. van der Heijde D, Lie E, Kvien TK, et al; Assessment of SpondyloArthritis international Society (ASAS). ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2009;68(12):1811-8.
29. Fernández-Espartero C, de Miguel E, Loza E, et al; ESPERANZA Study Group. Validity of the ankylosing spondylitis disease activity score (ASDAS) in patients with early spondyloarthritis from the Esperanza programme. *Ann Rheum Dis.* 2014;73(7):1350-5.
30. Godfrin-Valnet M, Prati C, Puyraveau M, et al. Evaluation of spondylarthritis activity by patients and physicians: ASDAS, BASDAI, PASS, and flares in 200 patients. *Joint Bone Spine.* 2013;80(4):393-8.
31. van der Heijde D, Braun J, Dougados M, et al. Sensitivity and discriminatory ability of the Ankylosing Spondylitis Disease Activity Score in patients treated with etanercept or sulphasalazine in the ASCEND trial. *Rheumatology (Oxford).* 2012;51(10):1894-905.
32. Machado PM, Landewé RB, van der Heijde DM. Endorsement of definitions of disease activity states and improvement scores for the Ankylosing Spondylitis Disease Activity Score: results from OMERACT 10. *J Rheumatol.* 2011;38(7):1502-6.
33. Machado P, Landewe R, Lie E, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. *Ann Rheum Dis.* 2011;70(1):47-53.

34. van der Heijde D, Braun J, Dougados M, et al. Sensitivity and discriminatory ability of the Ankylosing Spondylitis Disease Activity Score in patients treated with etanercept or sulphasalazine in the ASCEND trial. *Rheumatology (Oxford)*. 2012;51(10):1894-905. Epub 2012 Jul 06.
35. Machado P1, Landewé RB, Braun J, et al. MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor. *Ann Rheum Dis*. 2012;71(12):2002-5.
36. Wei JC. Treat-to-target in spondyloarthritis: implications for clinical trial designs. *Drugs*. 2014;74(10):1091-6.
37. Song IH, Hermann KG, Haibel H, et al. Consistently Good clinical response in patients with early axial spondyloarthritis after 3 years of continuous treatment with etanercept: longterm data of the ESTHER trial. *J Rheumatol*. 2014;41(10):2034-40.
38. Ramiro S, van der Heijde D, van Tubergen A, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Ann Rheum Dis*. 2014;73(8):1455-61.
39. Vastesaeger N, Cruyssen BV, Mulero J, et al. ASDAS high disease activity versus BASDAI elevation in patients with ankylosing spondylitis as selection criterion for anti-TNF therapy. *Reumatol Clin*. 2014;10(4):204-9.
40. Fagerli KM, Lie E, van der Heijde D, et al. Selecting patients with ankylosing spondylitis for TNF inhibitor therapy: comparison of ASDAS and BASDAI eligibility criteria. *Rheumatology (Oxford)*. 2012;51(8):1479-83.
41. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the german spondyloarthritis inception cohort. *Arthritis Rheum*. 2009;60(3):717-27.

42. Molto A, Granger B, Wendling D, et al. Brief report: nonsteroidal antiinflammatory drug-sparing effect of tumor necrosis factor inhibitors in early axial spondyloarthritis: results from the DESIR cohort. *Arthritis & Rheumatology*. 2015;67(9):2363-8.
43. Kiltz U, Sieper J, Rudwaleit M, et al. DGRh-S3-Leitlinie Axiale Spondyloarthritis inklusive Morbus Bechterew und Frühformen. *Z Rheumatol*. 2014;73 (Suppl 2):23-5.
44. Diel R, Hauer B, Loddenkemper R, et al. Empfehlungen für das tuberkulosescreening vor Gabe von TNF- $\alpha$ -Inhibitoren bei rheumatischen Erkrankungen. *Pneumologie*. 2009;63(6):329-34.
45. van Eijk IC, Nielen MM, van der Horst-Bruinsma I, et al. Aggressive therapy in patients with early arthritis results in similar outcome compared with conventional care: the STREAM randomized trial. *Rheumatology*. 2012;51(4):686-94.

## **Appendix A. Responsibilities of the Clinical Investigator**

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

**Appendix B. List of Protocol Signatories**

---

Name	Title	Functional Area
<i>Provided in a separate document</i>		

---

## **Appendix C. Assessment of SpondyloArthritis International Society (ASAS) Axial Spondyloarthritis Criteria for Classification**

In subjects with  $\geq 3$  months back pain<sup>^</sup> and age at onset  $< 45$  years

Sacroiliitis on imaging* plus $\geq 1$ SpA feature <sup>#</sup>	or	HLA-B27 Plus $\geq 2$ SpA feature <sup>#</sup>
---	----	--

<sup>#</sup> SpA features Inflammatory back pain Arthritis Enthesitis (heel) Uveitis Dactylitis Psoriasis Crohn's Disease/Ulcerative colitis Good response to NSAIDs Family history for SpA HLA-B27 Elevated CRP	<sup>*</sup> Sacroiliitis on imaging: active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA, or definite radiographic sacroiliitis according to modified New York criteria
---	---

<sup>^</sup> Almost daily back pain.

Adapted from: Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-83.



## Appendix D. Features of Spondyloarthritis

SpA Feature	Definition
Inflammatory back pain (IBP)	IBP according to experts: at least 4 out of 5 parameters present: 1. age at onset < 40 yrs; 2. insidious onset; 3. improvement with exercise; 4. no improvement with rest; 5. pain at night (with improvement upon getting up)
Arthritis	Past or present active synovitis diagnosed by a physician
Enthesitis (heel)	Heel enthesitis: past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus
Uveitis	Past or present uveitis anterior, confirmed by an ophthalmologist
Dactylitis	Past or present dactylitis, diagnosed by a physician
Inflammatory bowel disease	Past or present Crohn's disease or ulcerative colitis diagnosed by a gastroenterologist
Psoriasis	Past or present psoriasis (skin and/or nail lesions) diagnosed by a physician
Good response to NSAIDs	24 – 48 hours after a full dose of a NSAID the back pain is not present anymore or is much better
Family history for SpA	Presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces, and nephews) relatives of any of the following: a) ankylosing spondylitis, b) psoriasis, c) acute uveitis, d) reactive arthritis, e) inflammatory bowel disease
Elevated CRP	C-reactive protein concentration above upper normal limit in the presence of back pain; after exclusion of other causes for elevated CRP concentration
HLA-B27	Positive testing according to standard laboratory techniques
Sacroiliitis by MRI	Active inflammatory lesions of sacroiliac joints with definite bone marrow edema/osteitis, suggestive of sacroiliitis associated with spondyloarthritis as defined by ASAS

Adapted from: Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis.* 2009;68:777-83.

Adapted from: Dougados M, Braun J, Burgos Vargas R, et al. ASAS recommendations for variables to be collected in clinical trials/epidemiological studies of spondyloarthritis. *Ann Rheum Dis.* 2012;71(6):1103-4.

## **Appendix E. Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation**

Parameters used for the ASDAS:

1. Patient's assessment of total back pain
2. Patient global assessment of disease activity
3. Peripheral pain/swelling (BASDAI question 3)
4. Duration of morning stiffness (BASDAI question 6)
5. ESR in mm/hr

Calculation of ASDAS (*for reference only; the eCRF will be programmed to calculate the ASDAS*)

$ASDAS_{ESR} = 0.08 \times \text{total back pain} + 0.110 \times \text{patient global} + 0.09 \times \text{peripheral pain/swelling} + 0.07 \times \text{duration of morning stiffness} + 0.29 \times \sqrt{ESR}$

References:

Machado P, Navarro-Compan V, Landewé R, et al. Calculating the ankylosing spondylitis disease activity score if the conventional c-reactive protein level is below the limit of detection or if high-sensitivity c-reactive protein is used: an analysis in the DESIR cohort. *Arthritis Rheumatol.* 2015;67(2):408-13.

Lukas C, Landewé R, Sieper J, et al; Assessment of SpondyloArthritis international Society. Development of an ASAS endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis.* 2009;68:18-24.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68;ii1-ii44.

## Appendix F. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Numerical Rating Scale (NRS)

Please mark the box which represents your answer to each question relating to **the past week** (i.e., ☒)

1. How would you describe the overall level of fatigue/tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

3. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

6. How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
0 hr					1 hr					2 or more hrs

**Scoring of the BASDAI:**

BASDAI Score = 0.2 (Item 1 + Item 2 + Item 3 + Item 4 + Item 5 + Item 6)

2            2


The BASDAI Score has a maximum value of 10.

**References:**

Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21:2286-91.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68;ii1-ii44.

**Appendix G. Patient's Global Assessment of Disease Activity, Numerical Rating Scale (NRS)**

Please place a mark in the box below to indicate disease activity (i.e., )

What is your overall assessment of your disease activity during the last week?

0	1	2	3	4	5	6	7	8	9	10
none										very severe

**References:**

van der Heijde D, Dougados M, Davis J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum.* 2005;52(2):386-94.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68;ii1-ii44.

## Appendix H. Tender and Swollen Joint Counts

JOINT EVALUATION												
JOINT (Mark Correct Answer)	Patient Right						Patient Left					
	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
1. Temporomandibular	0	1	0	1	9	NA	0	1	0	1	9	NA
2. Sternoclavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
3. Acromio-clavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
4. Shoulder	0	1	0	1	9	NA	0	1	0	1	9	NA
5. Elbow	0	1	0	1	9	NA	0	1	0	1	9	NA
6. Wrist	0	1	0	1	9	NA	0	1	0	1	9	NA
7. Metacarpophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
8. Metacarpophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
9. Metacarpophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
10. Metacarpophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
11. Metacarpophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
12. Thumb Interphalangeal	0	1	0	1	9	NA	0	1	0	1	9	NA
13. Prox. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
14. Prox. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
15. Prox. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
16. Prox. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
17. Distal Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
18. Distal Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
19. Distal Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
20. Distal Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
21. Hip	0	1	-	-	9	NA	0	1	-	-	9	NA
22. Knee	0	1	0	1	9	NA	0	1	0	1	9	NA
23. Ankle	0	1	0	1	9	NA	0	1	0	1	9	NA
24. Tarsus	0	1	0	1	9	NA	0	1	0	1	9	NA
25. Metatarsophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
26. Metatarsophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
27. Metatarsophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
28. Metatarsophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA

JOINT EVALUATION												
	Patient Right						Patient Left					
JOINT (Mark Correct Answer)	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
29. Metatarsophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
30. Great Toe/Hallux	0	1	0	1	9	NA	0	1	0	1	9	NA
31. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
32. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
33. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
34. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA

## **Appendix I. Linear Bath Ankylosing Spondylitis Metrology Index (BASMI<sub>lin</sub>)**

1. Lateral lumbar flexion: patient stands with heels and buttocks touching the wall, knees straight, shoulders back, hands by the side. The patient is then asked to bend to the right side as far as possible without lifting the left foot/heel or flexing the right knee, and maintaining a straight posture, with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when patient bends to the side, is subtracted from the distance when the patient stands upright. The maneuver is repeated on the left side.

Left exact measurement (cm)\_\_\_\_\_ Right exact measurement (cm)\_\_\_\_\_

2. Tragus-to-wall distance: maintain same starting position as above. The distance between tragus of the ear and wall during maximal effort to draw the head back without raising the chin above its usually carrying level is measured on both sides to the nearest 0.1 cm, using a rigid ruler. Ensure no cervical extension, rotation, rotation, flexion or side flexion occurs.

Left exact measurement (cm)\_\_\_\_\_ Right exact measurement (cm)\_\_\_\_\_

3. Lumbar flexion (modified Schober): set marks in upright position at the level of the spinous process of L5 (found as the first process below the projected line across the back at the level of the top iliac crest) and 10 cm above the first mark. Measure distraction of the marks when the patient bends forward as far as possible, keeping the knees straight.

Exact measurement (cm)\_\_\_\_\_

4. Intermalleolar distance: patient supine on the floor or a wide plinth, with the knees straight and the feet pointing straight up. Patient is asked to separate legs along the resting surface as far as possible. Distance between medial malleoli is measured.

Exact measurement (cm)\_\_\_\_\_

Cervical rotation: patient supine on plinth, head in neutral position, forehead horizontal (if necessary head on pillow or foam block to allow this, must be



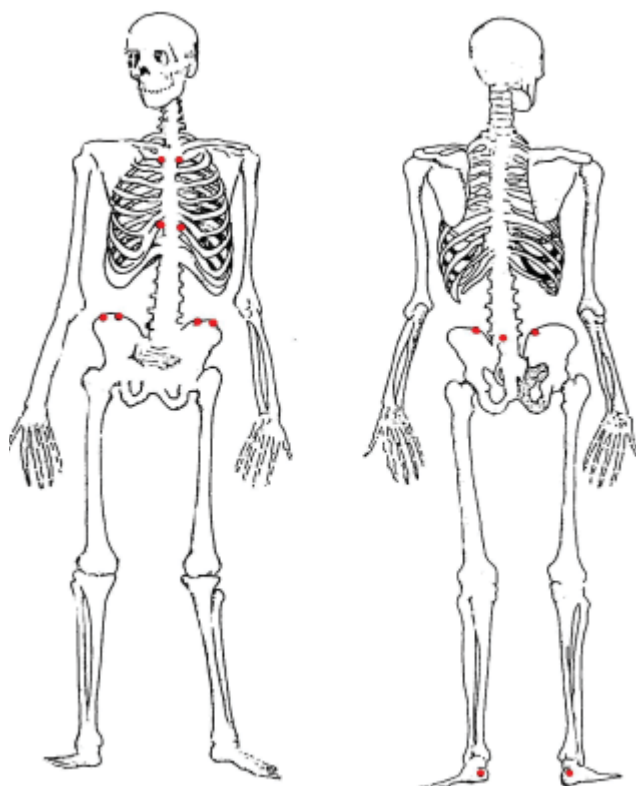
documented for future reassessments). Gravity goniometer placed centrally on the forehead. Patient rotates head as far as possible, keeping shoulders still, ensure no neck flexion or side flexion occurs. Rotational angled to the right and to the left is measured.

If you do not have a gravity goniometer: patient sits with shoulders to the wall. Place goniometer to the wall above the patient's head. Patient rotates head as described above. Examiner aligns goniometer branch parallel to sagittal plane of the head.

Left exact measurement (degrees)\_\_\_\_\_Right exact measurement (degrees)\_\_\_\_\_

Adapted from: van der Heijde D, et al. Proposal of a linear definition of the bath ankylosing spondylitis metrology index (BASMI) and comparison with the 2-step and 10-step definitions. Ann Rheum Dis. 2008;67;489-93. Epub 2007 Aug 29.

## Appendix J. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)




1<sup>st</sup> Costochondral joint left/right  
7<sup>th</sup> Costochondral joint left/right  
Posterior superior iliac spine left/right  
Anterior superior iliac spine left/right  
Iliac crest left/right  
5<sup>th</sup> Lumbar spinous process  
Proximal insertion of Achilles tendon left/right

### Reference:

Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis.* 2003;62:127-32.

## Appendix K. Bath Ankylosing Spondylitis Functional Index (BASFI), Numerical Rating Scale (NRS)

Please mark the box to indicate your level of ability with each of the following activities during the last week. (i.e., )

(An aid is a piece of equipment which helps you to perform an action or movement)

1. Putting on your socks or tights without help or aids (e.g., sock aid).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

2. Bending forward from the waist to pick up a pen from the floor without an aid.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

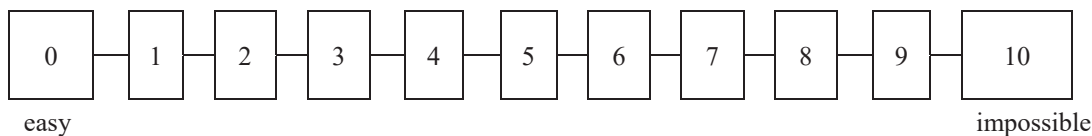
3. Reaching up to a high shelf without help or aids (e.g., helping hand).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

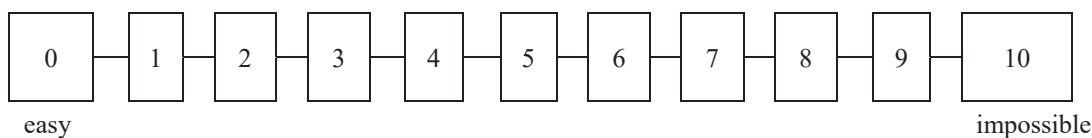
4. Getting up out of an armless dining room chair without using your hands or any other help.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

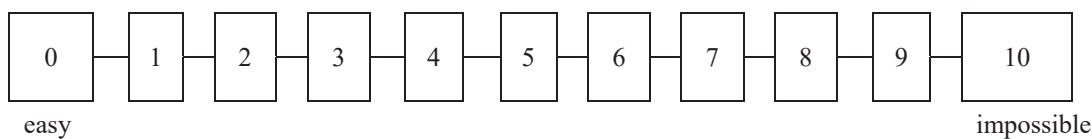
5. Getting up off the floor without help from lying on your back.



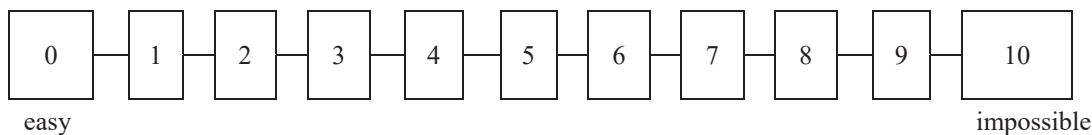
6. Standing unsupported for 10 minutes without discomfort.



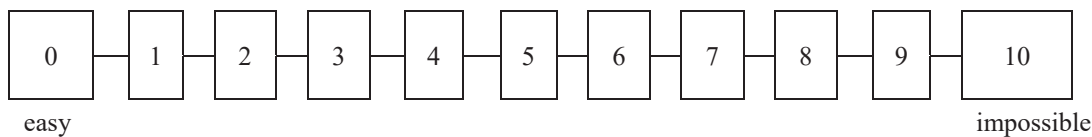
7. Climbing 12 – 15 steps without using a handrail or walking aid. One foot at each step.



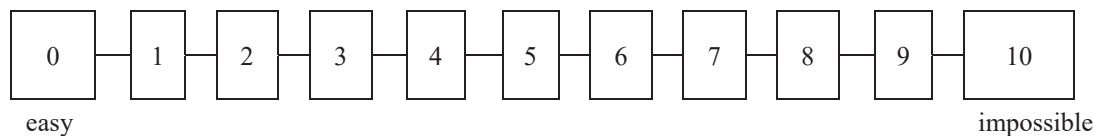
8. Looking over your shoulder without turning your body.



9. Doing physically demanding activities (e.g., physiotherapy exercises, gardening or sports).



10. Doing a full days activities, whether it be at home or at work.




References:

Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21:2281-5.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68:ii1-ii44.

## Appendix L. Physician's Global Assessment of Disease Activity, Numerical Rating Scale (NRS)

Please mark box to indicate disease activity (independent of the patient's self assessment)

(i.e., )


0	1	2	3	4	5	6	7	8	9	10
None										severe

### References:

van der Heijde D, Dougados M, Davis J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum.* 2005;52(2):386-94.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68;ii1-ii44.

**Appendix M. Patient's Assessment of Nocturnal Back Pain, Numerical Rating Scale (NRS)**

Please place a mark in the box below to indicate your answer (i.e., )

What is the amount of back pain at night that you experienced during the last week?


0	1	2	3	4	5	6	7	8	9	10
No Pain										Most severe pain

**References:**

van der Heijde D, Dougados M, Davis J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum.* 2005;52(2):386-94.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68;ii1-ii44.

**Appendix N. Patient's Assessment of Total Back Pain, Numerical Rating Scale (NRS)**

Please place a mark in the box below to indicate your answer (i.e., )

What is the amount of back pain that you experienced at any time during the last week?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Most severe pain


**References:**

van der Heijde D, Dougados M, Davis J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. *Arthritis Rheum.* 2005;52(2):386-94.

Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68;ii1-ii44.



**Appendix O. Patient's Global Assessment of Pain, Numerical Rating Scale (NRS)**

Please place a mark in the box below to indicate your answer (i.e., )

How much pain have you had because of your condition during the last week?

0	1	2	3	4	5	6	7	8	9	10
No Pain										pain as bad as it could be

---

**Appendix P. Assessment of Spondyloarthritis International Society (ASAS) Health Index (HI)**

Please answer all statements by placing one check mark per statement to indicate which response best applies to you **at this moment in time** taking into account your rheumatic disease (the term "rheumatic disease" contains all forms of spondyloarthritis including ankylosing spondylitis)

1. Pain sometimes disrupts my normal activities.  
☐ I agree  
☐ I do not agree
2. I find it hard to stand for long.  
☐ I agree  
☐ I do not agree
3. I have problems running.  
☐ I agree  
☐ I do not agree
4. I have problems using toilet facilities.  
☐ I agree  
☐ I do not agree
5. I am often exhausted.  
☐ I agree  
☐ I do not agree
6. I am less motivated to do anything that requires physical effort.  
☐ I agree  
☐ I do not agree

7. I have lost interest in sex.
- ☐ I agree
- ☐ I do not agree
8. I have difficulty operating pedals in my car.
- ☐ I agree
- ☐ I do not agree
9. I am finding it hard to make contact with people.
- ☐ I agree
- ☐ I do not agree
10. I am not able to walk outdoors on flat ground.
- ☐ I agree
- ☐ I do not agree
11. I find it hard to concentrate.
- ☐ I agree
- ☐ I do not agree
12. I am restricted in traveling because of my mobility.
- ☐ I agree
- ☐ I do not agree
13. I often get frustrated.
- ☐ I agree
- ☐ I do not agree
14. I find it difficult to wash my hair.
- ☐ I agree

☐ I do not agree

15. I have experienced financial changes because of my rheumatic disease.

☐ I agree

☐ I do not agree

16. I sleep badly at night.

☐ I agree

☐ I do not agree

17. I cannot overcome my difficulties.

☐ I agree

☐ I do not agree

Reference:

Kiltz U, van der Heijde D, Boonen A, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis. 2015;74:830-835.

**Appendix Q. Work Productivity and Activity Impairment Questionnaire: Axial Spondyloarthritis, V2.0 (Work Productivity and Activity Impairment [WPAI]: Axial Spondyloarthritis)**

The following questions ask about the effect of your axial spondyloarthritis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_NO \_\_\_\_YES

If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your axial spondyloarthritis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your axial spondyloarthritis. Do not include time you missed to participate in this study.*

\_\_\_\_ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

\_\_\_\_ HOURS

4. During the past seven days, how many hours did you actually work?

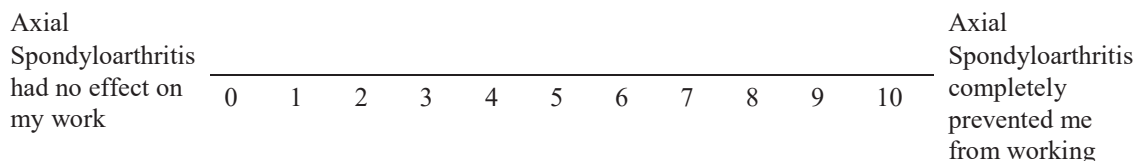
\_\_\_\_ HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your axial spondyloarthritis affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully

as usual. If axial spondyloarthritis affected your work only a little, choose a low number. Choose a high number if axial spondyloarthritis affected your work a great deal.

**Consider only how much axial spondyloarthritis affected productivity while you were working.**

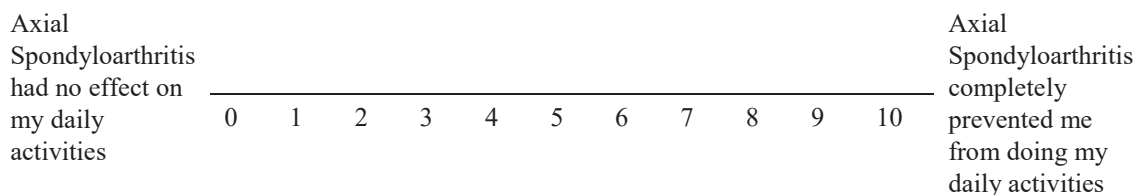


**CIRCLE A NUMBER**

6. During the past seven days, how much did your axial spondyloarthritis affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If axial spondyloarthritis affected your activities only a little, choose a low number. Choose a high number if axial spondyloarthritis affected your activities a great deal.*

**Consider only how much axial spondyloarthritis affected your ability to do your regular daily activities, other than work at a job.**



**CIRCLE A NUMBER**

Reference: Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353-65.

**Appendix R. European Quality of Life – 5 Dimension (EQ-5D) (United States [US] English Version)**

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

- |                                       |                          |
|---------------------------------------|--------------------------|
| I have no problems in walking about   | <input type="checkbox"/> |
| I have some problems in walking about | <input type="checkbox"/> |
| I am confined to bed                  | <input type="checkbox"/> |

**Self-Care**

- |   |                          |
|---|--------------------------|
| I have no problems with self-care               | <input type="checkbox"/> |
| I have some problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself             | <input type="checkbox"/> |

**Usual Activities (*e.g., work, study, housework, family or leisure activities*)**

- |  |                          |
|--|--------------------------|
| I have no problems with performing my usual activities   | <input type="checkbox"/> |
| I have some problems with performing my usual activities | <input type="checkbox"/> |
| I am unable to perform my usual activities               | <input type="checkbox"/> |

**Pain/Discomfort**

- |                                    |                          |
|------------------------------------|--------------------------|
| I have no pain or discomfort       | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort  | <input type="checkbox"/> |

**Anxiety/Depression**

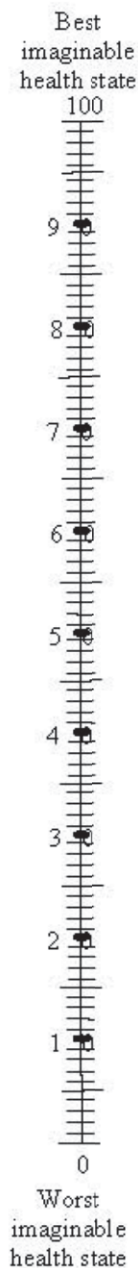
- |                                      |                          |
|--------------------------------------|--------------------------|
| I am not anxious or depressed        | <input type="checkbox"/> |
| I am moderately anxious or depressed | <input type="checkbox"/> |
| I am extremely anxious or depressed  | <input type="checkbox"/> |



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own  
health state  
today**



Reference: McDowell I, Newell C. The EuroQol Quality of Life Scale. Measuring health: a guide to rating scales and questionnaires. 2<sup>nd</sup> ed. 1996;9:480-3.

## Appendix S. Berlin Magnetic Resonance Imaging (MRI) Score for the Spine and the Sacroiliac Joints

	Grade 0	Grade 1	Grade 2	Grade 3
<b>Sacroiliac joints</b>				
Active inflammation (BMO of quadrant area)	Absent	Up to 33% of the quadrant area	33% – 66%	> 66%
Erosions (per quadrant)	Absent	Minor (one to two erosions)	Moderate (three to five single erosions)	Multiple (confluent erosions)
Fatty bone marrow deposition per quadrant	Absent	< 33%	33– 66%	>66%
Sclerosis (per joint)	Absent	Present	--	--
Ankylosis (per joint)	Absent	Present	--	--
<b>Spine</b>				
Active Inflammation (BMO of VU area)	Absent	< 33% of VU area	33% – 66%	> 66%
Erosions (% of the bone surface per VU)	Absent	present		
Fatty bone marrow deposition per VU	Absent	< 33%	33% – 66%	> 66%
Bone proliferation (per VU)	Absent	Syndesmophytes without bridging	Bridging syndesmophytes	Transdiscal ankylosis
Activity in facet joints (right and/or left)	Absent	present		--
Activity in Proc. spinosus	Absent	present		
Activity of soft tissue in posterior spinal sites	Absent	present		

BMO = bone marrow edema; VU = vertebral unit

Reference: Althoff CE, Sieper J, Song IH, et al. Active inflammation and structural change in early active axial spondyloarthritis as detected by whole-body MRI. Ann Rheum Dis. 2013;72:967-73.

## Appendix T. 70-Day Follow-Up Call – Sample

Site Name/Number: \_\_\_\_\_

Subject Number: \_\_\_\_\_

Please contact subjects who discontinued from adalimumab therapy 70 days following the end of Treatment period (Week 52) or study drug discontinuation.

Date of Call: \_\_\_\_\_

- ☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt.)
- ☐ No Events Reported
- ☐ NA – subject continued adalimumab therapy after the end of their study participation.

**List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. If needed, provide AE/SAE details on the AE worksheet attached. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event.)**

_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

**If events are listed above, your monitor will review and retrieve the appropriate eCRF pages during their next visit.**

Please fax all completed forms to:  
[Name] at XXX-XXX-XXXX

## **Appendix U. Injection Instructions – Sample Pre-Filled Syringe**

Instruction for subjects of the T2T arm escalated to Treatment Escalation step 2.

### **Subject Instructions**

**0.8 mL dose**

**(Administered as a single dose-pre-filled syringe)**

### **Protocol W15-679**

### **Tables of Contents**

Dosing Schedule

General Information & Supplies

Injection Procedures

### **Study Drug Dosing Schedule**

Subject Number: \_\_\_\_\_

You will require SC injections probably for the rest of the study. From now, you will receive a kit each visit containing 2 syringes.

When starting SC injections (at the first visit to receive study medication for this study) you will administer 1 injection at the clinic to allow site staff to view your injection technique.

Thereafter you will administer 1 injection at home every other week until the end of the study. *Note on clinic days, you must inject study drug after all study procedures are performed (not prior).*

You will not administer study medication at your last visit.

Please return all used and unused syringes, the sharps container and empty boxes to the clinic on your next visit. Used syringes should be placed in the special Sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject dosing sheet.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

### **General Information**

Pre-filled syringes with study medication will be labeled "Adalimumab."

Store all pre-filled syringes in your refrigerator at 2° to 8°C in the original container until it is used. NOT in the freezer. Should the syringes accidentally become frozen, call your study doctor's office.

Protect the study medication from light.

When traveling, study medication should be stored in a cool carrier with an ice pack.

Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.

Do not drop or crush the study medication. The prefilled syringe is glass.

Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.

**USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**

Save all study medications. ***Pre-filled syringes (used and unused) & empty boxes must be returned to the study center at each visit.*** Used syringes will be disposed of in a sharps container provided to you.

Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call**, \_\_\_\_\_ or proceed to your nearest emergency room.

Keep study medication, injection supplies, and all other medicines out of the reach of children.

## **Injection Procedures (PFS)**

### **1. Setting up for an injection**

Find a clean flat surface.

Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.

Take one kit with the prefilled syringe(s) of study drug from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.

Return any unused syringe(s) to the refrigerator.

You will need the following items for each dose:

study medication in pre-filled syringe

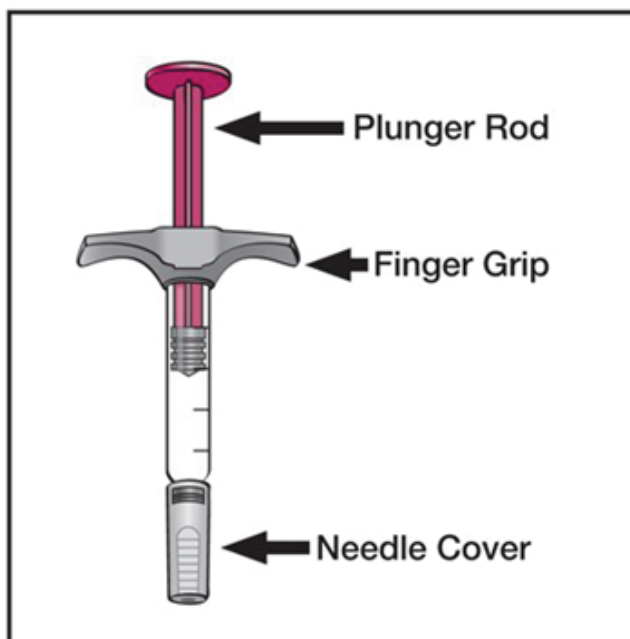
alcohol prep(s) or swab(s)

cotton ball(s) or gauze pad(s)

puncture-proof sharps container for prefilled syringe disposal

The diagram below shows what a prefilled syringe looks like. See Figure A.

**Figure A.**



If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your study drug comes in.

**Do not use** and call your study doctor if:

the seals on top and bottom of the carton are broken or missing.

the study medication labeling has an expired date. Check the expiration date on your study medication carton and do not use if the date has passed.

the prefilled syringe has been frozen or left in direct sunlight.

the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

For your protection, it is important that you follow these instructions.



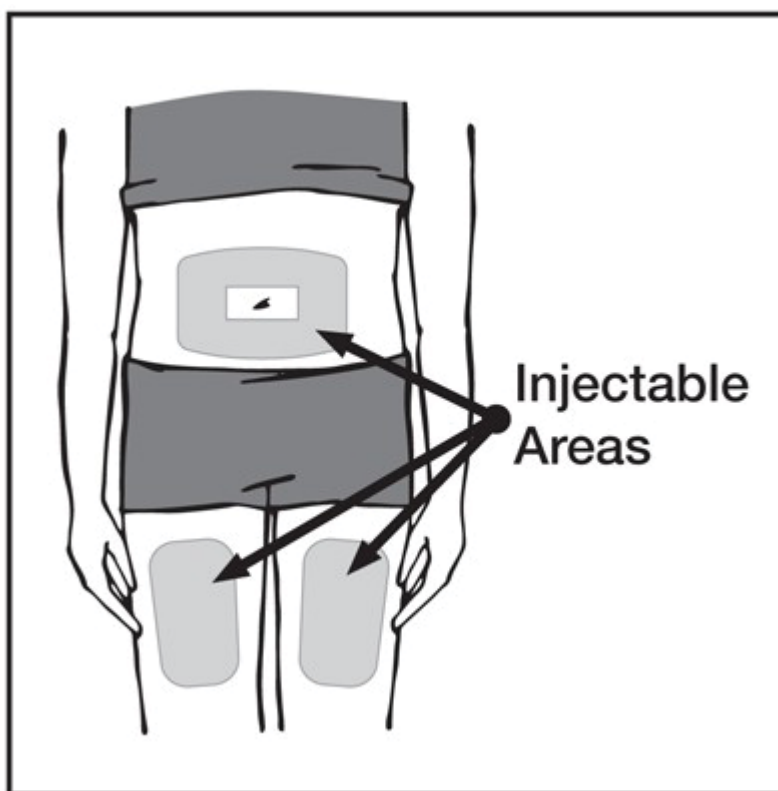
## 2. Choosing and preparing an injection site

Wash and dry your hands well

Choose an injection site:

- on the front of your thighs or
- your lower abdomen (belly). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel). See Figure B.

**Figure B.**



Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.

**Do not** inject into skin that is:

- sore (tender)
- bruised
- red
- hard
- scarred or where you have stretch marks

If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.

You may find it helpful to keep notes on the location of your injection sites.

Do not inject through your clothes.

Wipe the injection site with an alcohol prep (swab) using a circular motion.

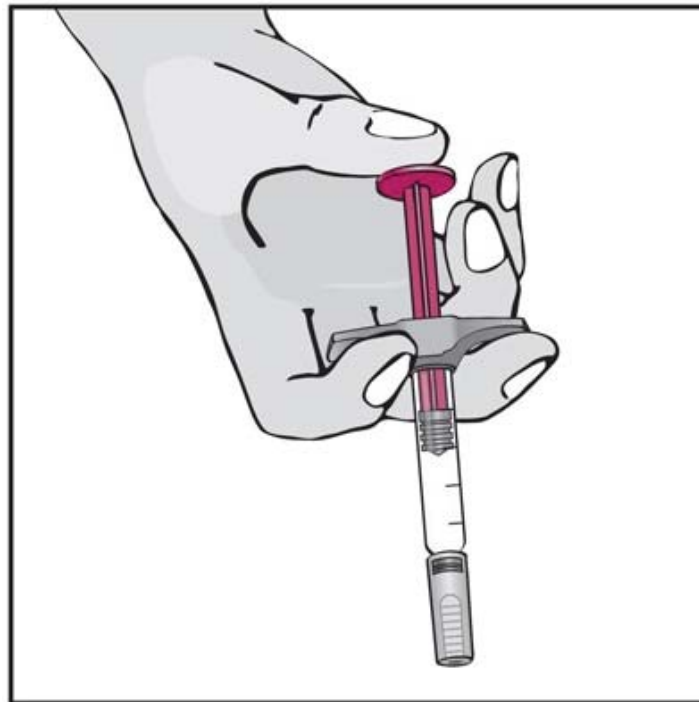
Do not touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

### **3. How to prepare your study drug dose for injection with a Prefilled Syringe**

Check the fluid level in the syringe:

- Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

**Figure C.**



Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg prefilled syringe. See Figure D.

**Figure D.**

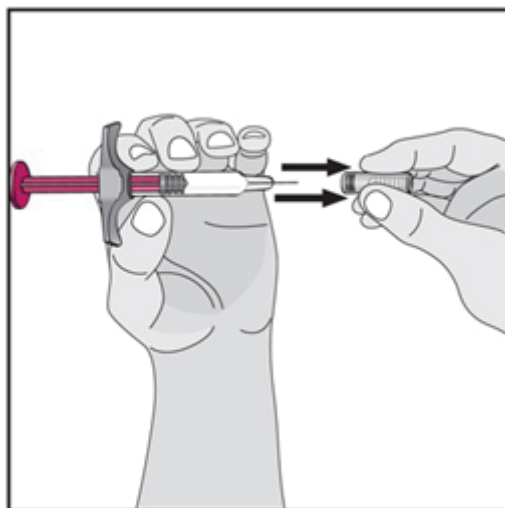


The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.

Remove the needle cover:

- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure E.
- Throw away the needle cover.

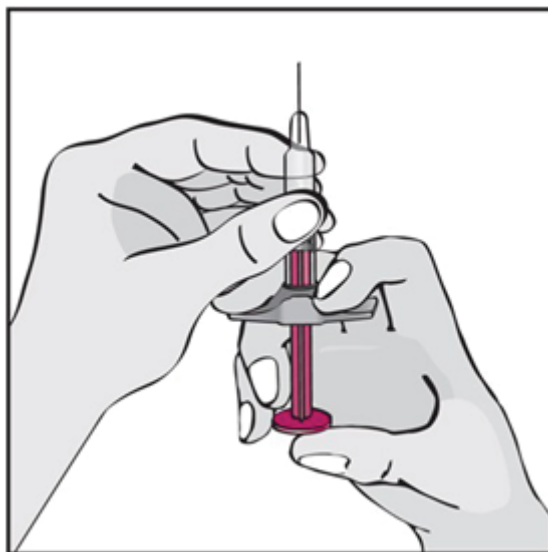
**Figure E.**



Do not touch the needle with your fingers or let the needle touch anything.

Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure F.

**Figure F.**



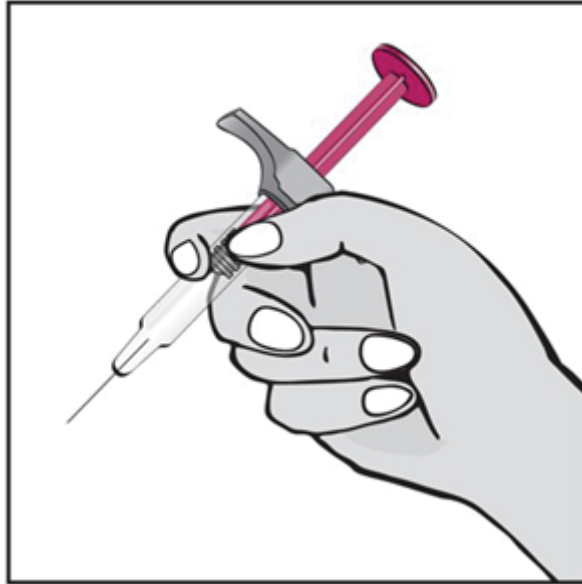
You may see a drop of liquid at the end of the needle. This is normal.

Do not shake the syringe.

#### **4. Injecting Study Drug**

Hold the body of the prefilled syringe in one hand between the thumb and index fingers.  
Hold the syringe in your hand like a pencil. See Figure G.

**Figure G.**



**Do not** pull back on the plunger at any time.

With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly. See Figure H.

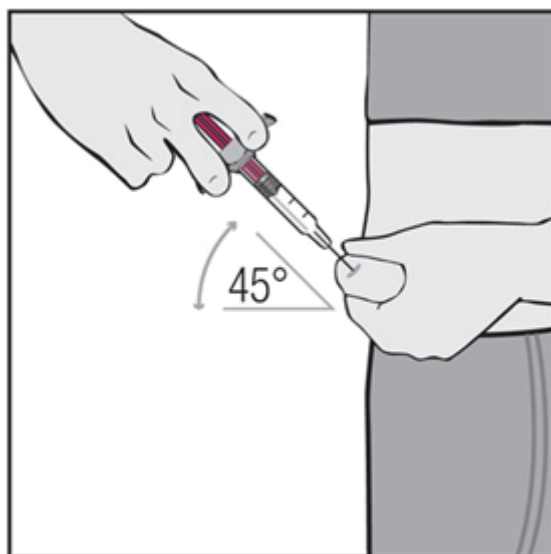
**Figure H.**



Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure I.



**Figure I.**



After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

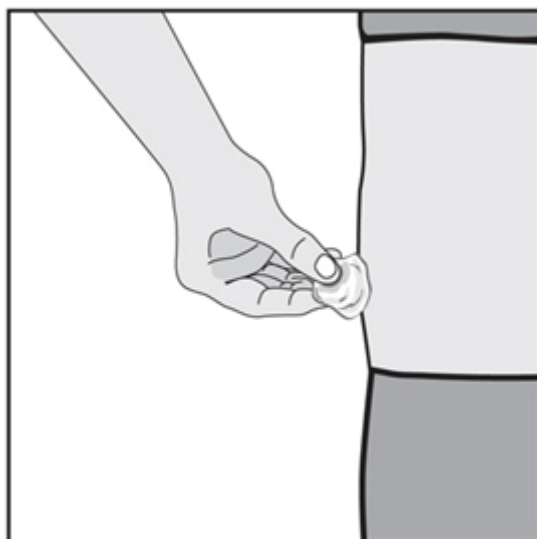
It means that you have entered a blood vessel.

Do not inject study drug.

Pull the needle out of the skin while keeping the syringe at the same angle.

Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure J.

**Figure J.**



**Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.

**Do not** rub the injection site. You may have slight bleeding. This is normal.

Repeat Steps 1 through 12 with a new prefilled syringe.

If no blood appears in the syringe:

Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.

Pull the needle out of the skin while keeping the syringe at the same angle.

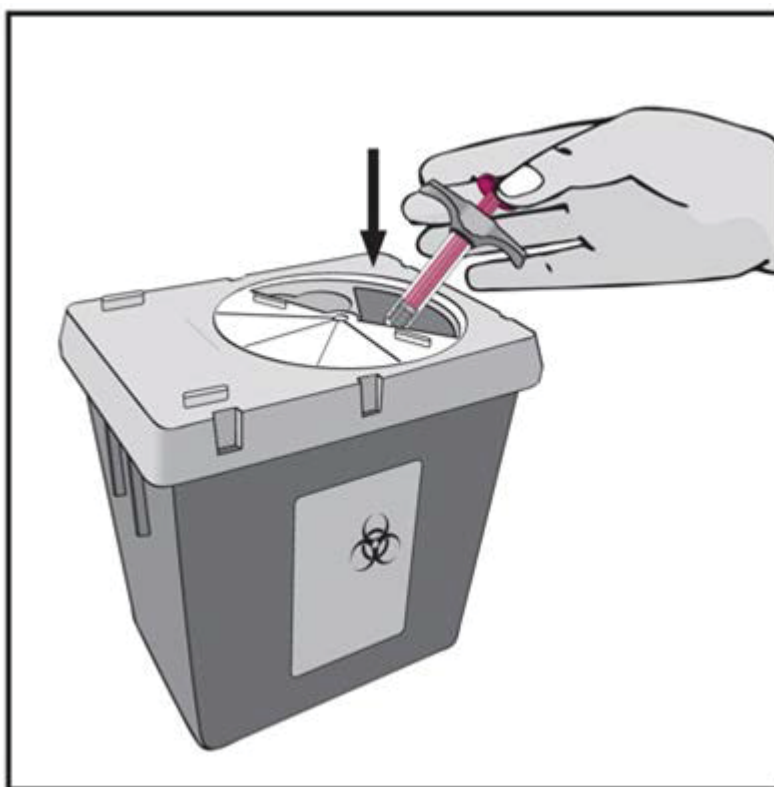
Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. **Do not** rub the injection site. You may have slight bleeding. This is normal.

Dispose of the syringe right away into your special sharps container. See Figure K.

Do not throw the needle, or syringe, in the household trash. Do not recycle.

Do not try to touch the needle.

**Figure K.**



For the safety and health of you and others, needles and used syringes must never be re-used.

Always keep the sharps container out of the reach of children.

The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.

When you go to your study visit tape the cap or lid of the sharps container down so it does not come off and take it to your visit. **Do not throw the container in the household trash. Do not recycle.**

## Appendix V. Subject Dosing Diary Sheet (Sample)

To be completed for every study dose administered. Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please record the date, time of study drug administration, kit number, dose administered, injection location, initials of person administering study medication, and any comments. Instructions on proper study medication administration will be provided by your study doctor and should be followed for every injection. Call the doctor's clinic if you are having problems administering your study medication.

Please bring your Sheet with you to each clinic visit.

If you have any questions or concerns at any time, please call the study coordinator or physician at the following number(s):

Subject Study Number: \_\_\_\_\_

Date day/mm/yr	Day or Week	Time of Study Drug Administration <sup>a</sup>	Kit Numbername	Dose (mL) Administered	Injection Site (Abdomen or Thigh)	Initials of Person Administering Study Medication	Comments
<u>31/MAY/16</u>	<u>EXAMPLE</u>	<u>09:30 hrs</u>	<u>123456</u>	<u>0.8 mL</u>	<u>abdomen</u>	<u>PG</u>	<u>Clinic injection</u>
	First injection	__ : __ hrs					
	2 weeks after 1 <sup>st</sup> injection	__ : __ hrs					
	4 weeks after 1 <sup>st</sup> injection	__ : __ hrs					
	6 weeks after 1 <sup>st</sup> injection	__ : __ hrs					
	8 weeks after 1 <sup>st</sup> injection	__ : __ hrs					

Date day/mm/yr	Day or Week	Time of Study Drug Administration <sup>a</sup>	Kit Numbername	Dose (mL) Administered	Injection Site (Abdomen or Thigh)	Initials of Person Administering Study Medication	Comments
	10 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	12 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	14 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	16 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	18 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	20 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	22 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	24 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	26 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	28 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	30 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	32 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	34 weeks after 1 <sup>st</sup> injection	--:-- hrs					

Date day/mm/yr	Day or Week	Time of Study Drug Administration <sup>a</sup>	Kit Numbername	Dose (mL) Administered	Injection Site (Abdomen or Thigh)	Initials of Person Administering Study Medication	Comments
	36 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	38 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	40 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	42 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	44 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	46 weeks after 1 <sup>st</sup> injection	--:-- hrs					
	48 weeks after 1 <sup>st</sup> injection	--:-- hrs					

a. Please note the time as full hours (24 hours scale) and minutes (e.g., 22:00 hrs etc.).

**Appendix W. Subject NSAID Dosing Diary Sheet (Sample)**

To be completed for every medication, other than study drug, administered as defined for T2T-Group. Please record the date of drug administration, dose administered, and any comments.

Please bring your Sheet with you to each clinic visit.

If you have any questions or concerns at any time, please call the study coordinator or physician at the following number(s):



**Subject Study Number:** \_\_\_\_\_

[illegible]

## Appendix X. Nonsteroidal Anti-Inflammatory Drug (NSAID) Intake Score

### ASAS NSAID Intake Score for Use in Clinical Trials / Epidemiological Studies of Spondyloarthritis

$$\text{NSAID Intake Score} = \text{NSAID daily dose (equivalent score*)} \times \frac{\text{Days of intake during period of interest} \times \text{Days of intake per week}}{\text{Period of interest in days}}$$

\* Equivalent score: a scale in which 0 = no intake, 100 = 150 mg diclofenac, 1000 mg naproxen, 200 mg aceclofenac, 400 mg celecoxib, 600 mg etodolac, 90 mg etoricoxib, 200 mg flurbiprofen, 2400 mg ibuprofen, 150 mg indometacin, 200 mg ketoprofen, 15 mg meloxicam, 400 mg phenylbutazone, 20 mg piroxicam, 20 mg tenoxicam

Example: during a period of interest of 6 months, the patient has taken diclofenac 75 mg daily during 4 months. The calculation of the ASAS NSAID intake score is as follows:

$$\text{NSAID Intake Score} = 50 \text{ (equivalent score of 75 mg diclofenac)} \times \frac{120 \text{ (4 months)} \times 7/7 \text{ (daily intake)}}{180 \text{ (6 months)}} = 33.3$$

Dougados M et al. Ann Rheum Dis 2011;70:249-51



When the exact number of days with NSAID intake is not known (usually when the interval of time between two visits exceeds 2 weeks), it is recommended to refer to the semiquantitative estimation. In this case, a score of 7/7 is proposed for the answer 'every day', 6/7 for > 5 days/week, 4/7 for > 3 to ≤ 5 days/week, 2/7 for > 1 to ≤ 3 days/week, 0.5/7 for ≤ 3 days/week and 0 if the patient did not take any NSAID during the period of interest.

Reference: Dougados M, Paternotte S, Braun J et al. ASAS recommendations for collecting, analyzing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis. 2011;70:249-51.

**Appendix Y. Recommended Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) to Treat Axial Spondyloarthritis**

**Dosage of NSAIDs Used to Treat Ankylosing Spondylitis**

drug	half-life (hours)	approved maximal daily dosage -normally for arthritis- (mg)
Aceclofenac <sup>#</sup>	about 4	200
Celecoxib	8-12	400
Diclofenac <sup>*</sup>	about 2	125-150
Etoricoxib <sup>#</sup>	about 22	90
Ibuprofen	1.8-3.5	2400-3200
Indomethacin <sup>*</sup>	about 2	150-200
Ketoprofen	1.5-2.5	200-300
Meloxicam	about 20	15
Naproxen	10-18	1000
Phenylbutazone <sup>#</sup>	50-100	600
Piroxicam	30-60	20

<sup>\*</sup>retard formula available

<sup>#</sup> not approved in the US

Adapted from Song IH et al. Arthritis Rheum 2008;58:929-38



Reference: Song IH, Poddubnyy DA, Rudwaleit M, et al. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. Ann Rheum Dis. 2008;58:929-38.