1.0 Title Page

Clinical Study Protocol M13-375

A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis

Incorporating Amendments 1 and 2

AbbVie Investigational Product:	Adalimumab
Date:	15 January 2015
Development Phase:	3b/4
Study Design:	This is a placebo-controlled, double-blind, randomized, multicountry, multicenter study.
EudraCT Number:	2012-000646-35
Investigators:	Multicenter Trial (Investigator information is on file at AbbVie)
Sponsor:	AbbVie Inc. Dept. R477, Bldg. AP4 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Contact:	[redacted]

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.

The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Include 6-MP in the list of stable DMARDs within the exclusion criteria.

  Rationale: azathioprine and 6-MP are considered equivalent.
- Increase screening period from less than or equal to 30 days to 6 weeks (42 days).

  Rationale: to allow sites sufficient time to complete all study screening procedures.
- Update IRT rounding rule in reference to ASDAS calculation.

  Rationale: more precisely calculate ASDAS to determine disease level at screening, remission (Weeks 16 – 28) and flare (Weeks 36 – 68).
- Addition of Optional Blood Sample Collection Sub-Study.

  Rationale: to learn more about non-radiographic axial spondyloarthritis (nr-axSpA), response to adalimumab, as well as individual variability in response to adalimumab.
- Correct typographical errors.

An itemized list of all changes made to the protocol under this amendment is found in Appendix X.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-375
Name of Study Drug: Adalimumab	**Phase of Development:** 3b/4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 15 January 2015
Protocol Title: A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis	
Objective: The objective of this study is to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given every other week (eow) subcutaneously (SC) in maintaining remission in subjects with non-radiographic axial Spondyloarthritis (nr-axSpA).	
Investigators: Multicenter	
Study Sites: Approximately 150 sites	
Study Population: Adult subjects with nr-axSpA and objective evidence of active inflammation in the sacroiliac (SI) joints or spine on MRI, or elevated high sensitivity C-reactive protein (hs-CRP).	
Number of Subjects to be Enrolled: Approximately 740	
Methodology: The study duration will include a 42-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40-week double-blind, placebo-controlled treatment period (Period 2), with an opportunity to receive at least 12 weeks of rescue therapy (subjects who flare at Weeks 60, 64 and 68 will be allowed 12 weeks of rescue therapy), and a 70-day follow-up phone call. Subjects in remission defined as meeting Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease (ASDAS < 1.300) at Weeks 16, 20, 24 and Week 28 will be randomized in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo during Period 2. Due to the importance of the Week 16, 20 and 24 visits, two or more missed visits during this time must be discussed with the AbbVie Medical Monitor prior to randomization. If a subject misses a single visit at Week 16, 20, or 24 the site will need to use the ASDAS parameters from the visit immediately prior to the missed visit. If a subject misses the Week 28 visit, the subject must be discontinued. Subjects not meeting the ASDAS Inactive Disease at Weeks 16, 20, 24 or Week 28 will be discontinued. Subjects may be discontinued as early as Week 20 if they do not meet the ASDAS remission criteria using the Week 16 parameters. No formal unblinded interim analysis is planned for this study that requires an adjustment to the *P* value. An interim analysis will be performed when all ongoing subjects have completed at least Week 28 of the study. The primary and secondary endpoints of the study from the double-blind period will be reported at the completion of the study. Subjects who flare in Period 2 (40-week double-blind period) will be allowed rescue therapy. Flare is defined as 2 consecutive study visits with ASDAS ≥ 2.100. Rescue therapy will consist of OL adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. After 12 weeks of rescue therapy with OL adalimumab eow, initiation of or change in a subject's concomitant medications for SpA including doses of DMARDs, corticosteroids, NSAIDs, and analgesics are permitted based on the investigator's medical judgment. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject age ≥ 18 years.
2. Subject with nr-axSpA fulfilling the Assessment of Spondyloarthritis International Society (ASAS) axial SpA classification criteria, but not fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis.
3. Subject has had an inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs) over a 4-week period in total at maximum recommended or tolerated doses, or has intolerance to or a contraindication for NSAIDs as defined by the Investigator.
4. Subject with objective evidence of active inflammation in the SI joints or spine on MRI or elevated hs-CRP at screening (elevated hs-CRP is defined as any level greater than the upper limit of normal for the lab).
5. Subject is a candidate for anti-TNF therapy based on the investigator's opinion.
6. Subjects must have baseline disease activity as defined by having an ASDAS ≥ 2.100 (note, sites will need to use the Screening Visit hs-CRP to calculate ASDAS at Screening and Baseline Visits with the remainder of parameters visit-specific), BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits.

Main Exclusion:

1. Subject fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis at or prior to the Screening Visit.
2. 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.
3. If entering the study on concomitant disease-modifying anti-rheumatic drugs (DMARDs), subject not on stable dose of methotrexate (≤ 25 mg per week) and/or sulfasalazine (≤ 3 g per day) and/or hydroxychloroquine (≤ 400 mg per day) for 28 days prior to the Baseline Visit. All other oral DMARDs, with the exception of azathioprine or mercaptopurine (6-MP) are prohibited within 28 days prior to the Baseline Visit.
4. If entering the study on concomitant azathioprine (AZA) or 6-MP, subject not on stable dose (AZA ≤ 150 mg per day or 6-MP ≤ 75 mg per day) for 28 days prior to the Baseline Visit or is on AZA or 6-MP and another concomitant immunosuppressive drug at study entry.
5. If entering the study on concomitant NSAIDs, tramadol, and/or non-opioid analgesics, subject not on stable doses for 14 days prior to the Baseline Visit.
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 not on stable dose of prednisone (≤ 10 mg per day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
8. Subject has been treated with intramuscular, intra-articular joint injection(s) or spinal/paraspinal injection(s) of corticosteroids in the preceding 28 days prior to the Baseline Visit.

Main Exclusion (Continued): 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 with extra-articular manifestations (e.g., inflammatory bowel disease, psoriasis, uveitis, etc.) that is not clinically stable for at least 30 days prior to study entry. 11. Subject has a history of fibromyalgia or inflammatory arthritis of a different etiology other than SpA (e.g., rheumatoid arthritis, gout, systemic lupus erythematosus, polyarticular or systemic juvenile idiopathic arthritis).	
Investigational Product:	Adalimumab
Dose:	40 mg eow
Mode of Administration:	SC
Reference Therapy:	Placebo
Dose:	eow
Mode of Administration:	SC
Duration of Treatment: Length of exposure will depend on remission or flare status (20 [first time ASDAS remission will be calculated] to 80 weeks of treatment). The duration of treatment will include a 28-week, OL period (adalimumab 40 mg eow), followed by a 40-week, randomized, double-blind period (adalimumab 40 mg eow versus placebo), with an opportunity to receive at least 12 weeks of rescue therapy (subjects who flare at Weeks 60, 64 or 68 will be allowed 12 weeks of rescue therapy and final study visit will be at Weeks 72, 76, or 80, respectively).	
Criteria for Evaluation: **Efficacy:** The primary efficacy variable is the proportion of subjects who do not experience a flare by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS $\geq$ 2.100. Secondary efficacy variables include the following: At 12 weeks after initiation of Rescue Therapy • ASDAS Inactive Disease (ASDAS < 1.300) • ASDAS Major Improvement (a change from baseline $\leq$ –2.000) • ASDAS Clinically Important Improvement (a change from baseline $\leq$ –1.100)	

Efficacy (Continued):

- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
  - ASAS20 response: improvement of ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit)
    - Patient's Global Assessment – Represented by the PTGA-disease activity NRS score (0 to 10)
    - Pain – Represented by the patient's assessment of total back pain NRS score (0 to 10)
    - Function – Represented by the BASFI NRS score (0 to 10)
    - Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10])
  - ASAS40 response: improvement of ≥ 40% and absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in ≥ 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain
  - ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20
  - ASAS 5/6 response: 20% improvement from Baseline in 5 out of the following 6 domains: BASFI, patient's assessment of total back pain, PTGA-disease activity, inflammation (mean of items 5 and 6 of the BASDAI), lateral lumbar flexion from BASMI, and hs-CRP
- Bath AS Disease Activity Index 50 (BASDAI50)
- Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

At Week 28 and Week 68

- ASDAS Inactive Disease
- ASDAS Major Improvement
- ASDAS Clinically Important Improvement
- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
- BASDAI50
- HAQ-S

At Week 68

- Time to flare defined as ASDAS ≥ 2.100 at 2 consecutive visits
- Time to partial flare defined as ASDAS ≥ 1.300 but < 2.100 at 2 consecutive visits
- Proportion of subjects who reach flare definition
- Proportion of subjects who reach partial flare definition

<u>Other Efficacy Variables</u>

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of Total back pain
- Bath AS Functional Index (BASFI)
- Inflammation/Morning Stiffness (mean of BASDAI questions 5 and 6)

Efficacy (Continued):

- Bath AS Disease Activity Index (BASDAI)
- ASDAS
- hs-CRP
- Linear Bath AS Metrology Index ($BASMI_{lin}$)
- Swollen Joint Count (66 joints)
- Tender Joint Count (68 joints)
- MASES
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Pain
- Patient's Assessment of Nocturnal Back Pain
- Anterior Uveitis
- Short Form-36v2 Health Survey questionnaire
- EQ-5D
- Work Productivity and Activity Impairment – Axial Spondylorarthritis (WPAI-axial SpA)
- SPARCC scores for MRI of the SI joint and spine
- Proportion of subjects who regain remission on rescue therapy
- Time to regain remission on rescue therapy

Exploratory Variables:

Each subject will have blood drawn for biomarkers at the following time points: Baseline, Weeks 28, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit. The final set of biomarkers to be analyzed may include the following:

- DKK-1
- Sclerostin
- BMP-2
- BMP-7

The final selection of biomarkers for analysis will be based on both insights gained in the sub-study and available scientific knowledge at study completion.

Pharmacokinetic:

Each subject will have blood drawn for serum adalimumab concentration and anti-adalimumab antibody (AAA) at the following time points: Baseline, Weeks 12, 28, 36, 52, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit.

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, vital signs, physical examination (if required) and laboratory tests.

Statistical Methods:

Efficacy:

The primary efficacy variable is the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study between the adalimumab and placebo groups. Analysis will be performed using a two-sided chi squared test with an $\alpha = 0.05$. Subjects with missing primary efficacy endpoint response at Week 68 will be treated as non-responders, i.e., a "non-responder imputation" criterion will be used for missing data. Descriptive statistics will also be provided for primary and secondary efficacy variables.

Pharmacokinetic:

For each scheduled time of measurement, summary statistics will be provided for the adalimumab serum concentration data by treatment group. The adalimumab concentration data may be analyzed using nonlinear mixed effects modeling approach. The percentage of subjects with AAA will be reported.

Safety:

Safety analyses will be carried out using the safety population, which includes all subjects who received at least one dose of study medication. 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 first dose of the study medication, and up to within 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 body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. In addition, summary of AEs by severity and relationship to study drug will be presented. Serious, severe, or AEs that lead to premature study discontinuation will be listed.

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 prior to the first dose of study drug 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:

Assuming that 50% of subjects treated with adalimumab will not experience any flare up to Week 68, 120 subjects per arm are required for the double-blind period (Period 2) (with an adjustment for a drop-out rate of no more than 30%) is targeted to result in at least 90% power for detecting 25% difference at Week 68 primary endpoint between adalimumab and placebo based on a two-sided test with significance level 0.05.

It is assumed that approximately 33% of the subjects enrolled into the OL period (Period 1) would meet ASDAS Inactive Disease at Weeks 16, 20, 24 and Week 28; therefore, a total of approximately 740 subjects would be required to be enrolled in order to have sufficient number of subjects (i.e., 120 subjects per arm) for the double-blind period. Study enrollment will be closed prior to reaching 740 subjects should a sufficient number of subjects fulfill remission criteria and be available for randomization at the end of Period 1 prior to full enrollment.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

6-MP	6-mercaptopurine
AAA	Anti-adalimumab Antibody
ADA	Adalimumab
AE	Adverse Event
ANA	Antinuclear Antibody
ANOVA	Analysis of Variance
AP	Anteroposterior
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AZA	Azathioprine
BASDAI	Bath AS Disease Activity Index
BASFI	Bath AS Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacille Calmette-Guérin
BM	Biomarker
BMP	Bone Morphogenetic Protein
BUN	Blood Urea Nitrogen
CD	Crohn's disease
CDC	Centers for Disease Control
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CXR	Chest X-ray
DKK-1	Dickkopf-1
DMARD	Disease-Modifying Anti-Rheumatic Drugs
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid

eow	Every Other Week
EQ-5D	European Quality of Life – 5 Dimension
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HAQ-S	Health Assessment Questionnaire modified for the Spondyloarthropathies
HBc Ab	Hepatitis B core antibodies
HBs Ab	Hepatitis B surface antibodies
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen-B27
hs-CRP	High Sensitivity C-reactive Protein
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IGRA	Interferon-Gamma Release Assay
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LOCF	Last Observation Carried Forward
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NONMEM	Non-Linear Mixed Effect Modeling
nr-axSpA	Non-radiographic Axial Spondyloarthritis
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drug
NYHA	New York Heart Association
OL	Open-label
PA	Posterior-anterior
PG	Pharmacogenetic

PK	Pharmacokinetic
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
SF-36V2	Short Form-36 Health Status Survey Version 2
SGOT/AST	Serum Glutamic-oxaloacetic Transaminase
SGPT/ALT	Serum Glutamic-pyruvic Transaminase
SI	Sacroiliac
SJC	Swollen Joint Count
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SRM	Serum
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
URL	Uniform Resource Locator
US	United States
WBC	White Blood Cell
WPAI-axial SpA	Work Productivity and Activity Impairment – Axial Spondylorarthritis

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3.0 Introduction

3.1 Non-Radiographic Axial Spondyloarthritis

Spondyloarthritis (SpA) is a group of diseases that share common clinical, radiographic, and genetic features.[1] This includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, enteropathic or inflammatory bowel disease related arthritis, and undifferentiated SpA. Because there is an overlap of symptoms among these diseases, there is some variability in the way physicians may interpret and apply diagnoses in clinical practice. A more universally consistent way of categorizing SpA patients would be to define them by their primary clinical manifestation of axial or peripheral SpA.

Axial SpA encompasses a spectrum of disease manifestations which has been split into 2 categories—AS and non-radiographic axial SpA (nr-axSpA)—due to the 1984 modified New York criteria which required the presence of sacroiliitis on plain radiographs for the classification of AS.[2,3] Clinically, patients with AS and nr-axSpA have comparable clinical manifestations and burden of disease[4] with the sole differentiating characteristic between the 2 categories of axial SpA being the presence of sacroiliitis visualized by plain radiographs.

The Assessment of SpondyloArthritis international Society (ASAS) has proposed and validated new classification criteria for patients with axial SpA and for those with peripheral SpA.[5,6] The rationale for the development of the ASAS axial SpA criteria was to develop criteria that were applicable to patients with or without radiographic sacroiliitis.[7] These criteria included not only plain x-rays but also Magnetic Resonance Imaging (MRI) as imaging modalities for classification.[5] These criteria were meant to facilitate the conduct of clinical trials in nr-axSpA which was considered an unmet need by the experts who developed the criteria.[5,7]

3.2 Current Treatments

There is an unmet medical need for treatment in nr-axSpA patients who fail nonsteroidal anti-inflammatory drug (NSAIDs). Registry and clinical trial data indicate that AS and

nr-axSpA patients have comparable burden of disease that requires treatment irrespective of radiographic progression.[4,8,9] NSAIDs are considered first line therapy for all axial SpA patients.[10,11] Traditional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine (SSZ) have not been shown to be effective for axial SpA.[12,13] For AS patients who continue to have active disease despite NSAIDs, adalimumab is an approved therapy. However, nr-axSpA patients who may have the same signs, symptoms, and level of disease activity as AS patients who qualify for adalimumab therapy, currently have no other treatment alternative to NSAIDs. This led to the clinical development program for adalimumab in nr-axSpA patients who have moderate to severe disease as indicated by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 4 or greater despite treatment with NSAIDs.
Study M10-791 (ABILITY I) was a randomized, placebo controlled clinical trial of adalimumab in patients with nr-axSpA who have failed at least 1 NSAID, or have an intolerance to or contraindication for NSAIDs. At Week 12, the ASAS40 response was statistically significant for adalimumab compared to placebo – 36.3% versus 14.9% ($P < 0.001$).

There are current data to suggest that continuous anti-tumor necrosis factor (anti-TNF) therapy is needed for nr-axSpA patients to maintain clinical response or remission over time. In an investigator-initiated, randomized, placebo-controlled study of adalimumab in 46 nr-axSpA subjects, 23 subjects attained an ASAS40 response and 9 reached ASAS partial remission after 52 weeks.[9,14] Adalimumab was discontinued in these 23 subjects, and the subjects were followed for 1 year without adalimumab treatment. Disease flare, defined as no longer reaching an ASAS40 response, resulted in retreatment with adalimumab. Over the 1-year observation period without treatment, 19 of 23 (83%) of the initial ASAS40 responders had a disease flare, while only 4 of 23 (17%) maintained their response. Mean duration of ASAS40 response until flare in these 19 patients was 14.8 weeks. Seven of the 9 (78%) subjects initially achieving ASAS partial remission relapsed during the 1-year observation period without treatment. After restarting treatment with adalimumab, 9 of 18 (50%) subjects reached ASAS40 and 4 of 18 (22.2%) subjects attained ASAS partial remission after 12 weeks of retreatment. Similar results

were noted in the ESTHER trial.[15] This trial included 76 active axial SpA subjects with disease duration < 5 years and active inflammation in either the sacroiliac (SI) joints or spine on whole body MRI at Baseline, 39 of whom fulfilled modified New York criteria for AS. Subjects received either etanercept (n = 40) or SSZ (n = 36) for 48 weeks. At 48 weeks, 33% (13/40) of etanercept and 11% (4/36) of SSZ subjects in study remission (defined by ASAS remission and absence of inflammation in the spine and SI joints on MRI) were taken off therapy and observed for flares. In the etanercept group, 9 subjects flared (BASDAI worsening of ≥ 2 points as compared to Week 48) after a mean of 24.4 weeks after stopping etanercept, and in the SSZ group, 3 patients flared after a mean of 39.6 weeks. Approximately half of the subjects flaring after etanercept withdrawal responded to retreatment with etanercept (ASAS remission 56%; study remission 44%).

3.3 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (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-α but not to lymphotoxin-α (TNF-β).

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 (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in the United States (US) and European Union (EU) for the treatment of rheumatoid arthritis (RA) in 2002 and 2003, respectively. Additional indications have been approved in the US and EU including Psoriasis, PsA, AS, Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), and Polyarticular Juvenile Idiopathic Arthritis. In addition, an indication for nr-axSpA and Pediatric Enthesitis-Related Arthritis has been approved in the EU. 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 an 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 6.5 under Adverse Event (AE) Reporting.

3.5 Differences Statement

This is the first adequately powered study to evaluate the efficacy and safety of continuing therapy with adalimumab 40 mg every other week (eow) subcutaneous (SC) versus withdrawing therapy in maintaining remission in subjects with nr-axSpA.

3.6 Benefits and Risks

There is an unmet medical need for the treatment of nr-axSpA. The utility of TNF blockade with adalimumab in nr-axSpA has been established in a randomized controlled trial 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 including the associated indication of AS. 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. For Study M13-375, to ensure nr-axSpA subjects are appropriate candidates for anti-TNF therapy subjects are required to meet a minimum level of disease activity at baseline (ASDAS $\geq$ 2.100, BASDAI $\geq$ 4, Patient's Assessment of Total Back Pain score $\geq$ 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), and have had an inadequate response to at least 2 NSAIDs. 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 nr-axSpA is that it is designed to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given eow SC in maintaining remission in subjects with nr-axSpA. As nr-axSpA is associated with considerable pain, reduction in health-related quality of life, and work impairment it would benefit patients to know if persistent adalimumab therapy is required to maintain remission.

4.0 Study Objective

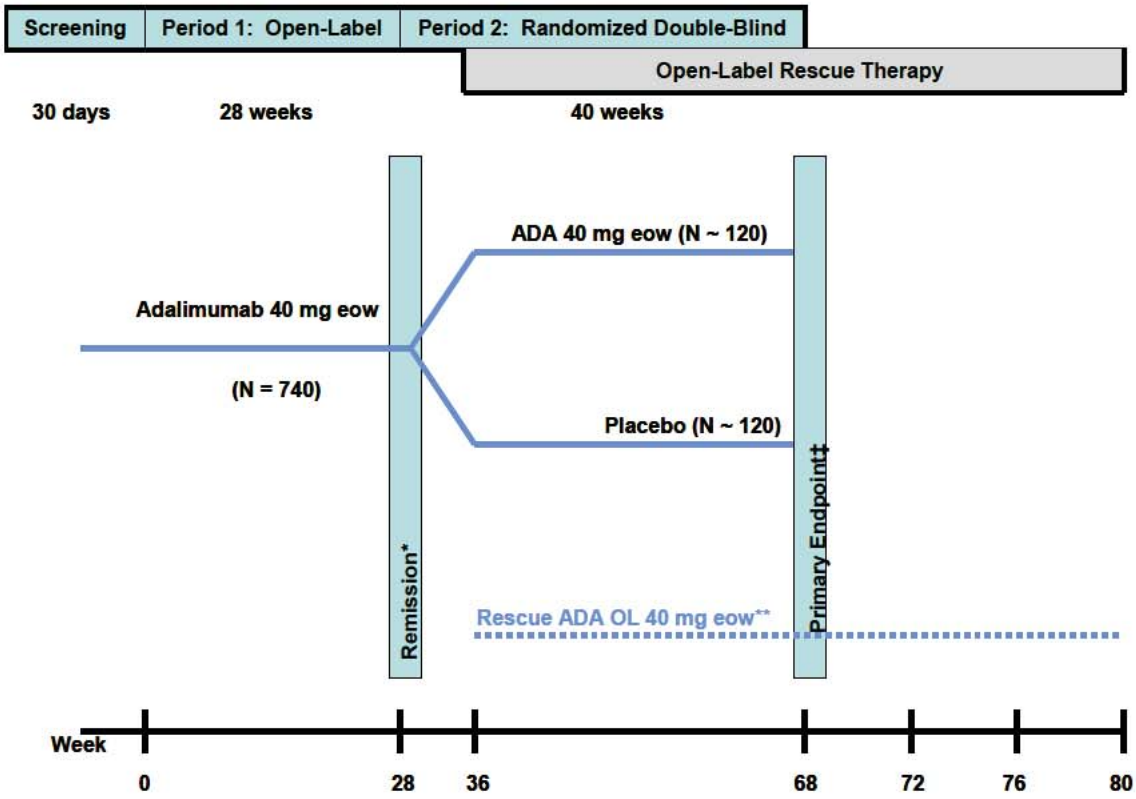
The objective of this study is to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given eow SC in maintaining remission in subjects with nr-axSpA.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study duration will include a 42-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40 week double-blind placebo controlled eow treatment period (Period 2) with an opportunity to receive at least 12 weeks of rescue therapy (subjects that flare at Weeks 60, 64 or 68 will be allowed 12 weeks of rescue therapy and final visits will be 72, 76 or 80 respectively), plus a 70-day follow-up phone call. The study design schematic is presented in Figure 1. Length of exposure will depend on remission or flare status (20 [first time ASDAS remission will be calculated] to 80 weeks of treatment).

Figure 1. Study Design Schematic



* Subjects who meet remission criteria (ASDAS inactive disease < 1.300) at Weeks 16, 20, 24 and 28 will be randomized to Period 2. Subjects not meeting remission criteria will be discontinued at Weeks 20, 24 or 28.

** Subjects who flare (ASDAS ≥ 2.100 for 2 consecutive study visits) during the double-blind period (Period 2) can receive rescue therapy with OL ADA 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of this study. The earliest time a subject can meet the flare criteria would be at Week 36 since a subject would need to have 2 consecutive visits with ASDAS ≥ 2.100. Subjects who flare at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80 respectively.

‡ Primary Endpoints: Proportion of subjects who do not experience a flare by Week 68 of the study. Study participation will end at Week 68 for subjects who meet the primary endpoint.

Note: Study enrollment will be closed prior to reaching 740 subjects should a sufficient number of subjects fulfill remission criteria and be available for randomization at the end of Period 1 prior to full enrollment.

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 cannot be enrolled until the Anteroposterior (AP) Pelvis x-ray images have been centrally read for the presence/absence of sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3-4 unilaterally and the report is available to the site, and the site also has the following results to determine fulfillment of the ASAS axial SpA criteria and objective evidence of active inflammation: 1) human leukocyte antigen-B27 (HLA-B27), 2) report from the central reading of the MRI of the SI joints and spine and 3) hs-CRP. *Note: The AbbVie Medical Monitor may allow on a case-by-case basis, a subject to be enrolled without having the results of the MRI, HLA-B27 and/or hs-CRP as the results of these procedures may not be necessary to determine eligibility. Discussion must be documented prior to enrolling the subject.*

Subjects that 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 *(Note: one additional re-screen may be approved by the AbbVie Medical Monitor on a case-by-case basis)*. 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 a purified protein derivative (PPD) test or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-tube test or T SPOT TB test), chest x-ray (CXR), MRI of the SI joints and spine, AP pelvis x-ray, HLA-B27, Antinuclear Antibody (ANA) or electrocardiogram (ECG), these tests will not be required to be repeated for the re-screening provided the conditions noted in

Section 5.3 are met and no more than 30 days has passed for the MRI of the SI joints and spine, 3 months (90 days) have passed for the PPD test or IGRA test, CXR and ECG and 1 year (365 days) for the AP pelvis x-ray. There is no need to redraw the HLA-B27 or ANA once the results are available from the central laboratory chosen for this study. If re-screening requires a MRI, sites are required to contact the AbbVie Medical Monitor to confirm if subjects should or should not be re-screened.

Open-Label Period (Period 1)

This period will begin at the Baseline Visit (Day 1) and will end at the Week 28 Visit. The Baseline Visit and Day 1 should be the same day. At this visit, subjects who meet the enrollment (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 dispensed OL 40 mg adalimumab to be taken eow. During this period of the study, the subjects will visit the study site on Weeks 2, 4, 8, 12, 16, 20, 24 and 28 or if they terminate early from the study. The last OL dose is given at Week 26.

The ASDAS calculation in Period 1 (OL) will be done at Weeks 20, 24 and 28 (prior to randomization). All ASDAS visit parameters listed in Appendix E should be used from each study visit (with the possible exception of hs-CRP as described below).

At Week 20, sites will enter the ASDAS parameters into IVRS/IWRS using the IVRS/IWRS worksheets provided separately. At Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

At Week 24, sites will enter the ASDAS parameters into IVRS/IWRS using the IVRS/IWRS worksheets provided separately. At Week 24, calculation of the Week 20 ASDAS will be done using the Week 20 visit parameters including the Week 20 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

At Week 28, sites will enter the ASDAS parameters into IVRS/IWRS using the IVRS/IWRS worksheets provided separately. At Week 28, calculation of the Week 24 ASDAS will be done using the Weeks 24 parameters including the Week 24 hs-CRP; the Week 28 ASDAS will be done using Week 28 parameters and the Week 24 hs-CRP (as the Week 28 results will not be available). If any of these time points do not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Subjects may be discontinued as early as Week 20 if they do not meet the ASDAS remission criteria using the Week 16 parameters.

Due to the importance of the Week 16, 20 and 24 visits, two or more missed visits during this time must be discussed with the AbbVie Medical Monitor prior to randomization. If a subject misses a single visit at Week 16, 20 or 24 the site will need to use the ASDAS parameters from the visit immediately prior to the missed visit. If the subject misses the Week 28 visit, the subject must be discontinued.

If a subject has an elevated hs-CRP which the investigator believes to be secondary to an AE and not due to nr-axSpA at Weeks 16, 20, 24 or 28, sites may repeat the hs-CRP test prior to the subject's next scheduled visit following a discussion with the AbbVie Medical Monitor. The repeat hs-CRP results should be available to the site prior to the subject's next scheduled visit and will replace the visit-specific hs-CRP in the ASDAS calculation. Instances where AE-related hs-CRP elevation spans more than one study visit will be addressed on a case-by-case basis. *Note: the AE should be reported in EDC prior to discussion with the AbbVie Medical Monitor.*

Double-Blind Period (Period 2)

This period will begin at Week 28 and will end at Week 68. Subjects in remission defined as meeting Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease (ASDAS < 1.300) at Week 16, 20, 24 and Week 28 (described above) will be randomized in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo.

During this period of the study, the subjects will visit the study site on Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 or if they discontinue early from the study. Subjects who flare, defined as 2 consecutive study visits with ASDAS ≥ 2.100 in Period 2 (40-week double-blind period) will be allowed rescue therapy. The earliest time a subject can meet the flare criteria would be at Week 36 since a subject would need to have 2 consecutive visits with ASDAS ≥ 2.100. The hs-CRP from the prior visit will be used to calculate the ASDAS for both the prior visit and the current visit with the remainder of the ASDAS parameters visit-specific. *(Note: site will need to enter the ASDAS parameters used for calculation outlined in Appendix E into IVRS/IWRS at Weeks 36 for that visit as well as the previous visit. Source worksheets will be available for sites to use during the IVRS/IWRS entry)*. For subjects who meet flare criteria during Period 2 and start rescue therapy with OL adalimumab, further calculation of ASDAS is not required. For any subject missing 2 consecutive visits within the double-blind period (Period 2), the site must contact the AbbVie Medical Monitor for discussion regarding the subject's continued participation in the study.

Following the Week 28 visit, if a subject has an elevated hs-CRP which the investigator believes to be secondary to an AE and not due to nr-axSpA, the site may repeat the hs-CRP test prior to the subject's next scheduled visit following a discussion with the AbbVie Medical Monitor. The repeat hs-CRP results should be available to the site prior to the subject's next scheduled visit and will replace the visit-specific hs-CRP in the ASDAS calculation. Instances where AE-related hs-CRP elevation spans more than one study visit will be addressed on a case-by-case basis. *Note: the AE should be reported in EDC prior to discussion with the AbbVie Medical Monitor.*

Rescue Therapy

For those subjects who meet the flare criteria during the double-blind period (Period 2), rescue therapy will consist of OL adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. After 12 weeks of rescue therapy with OL adalimumab eow, initiation of or change in a subject's concomitant medications for SpA including doses of DMARDs, corticosteroids, NSAIDs,

and analgesics are permitted based on the investigator's medical judgment. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab eow will be provided for 12 weeks and the final study visit will be at Weeks 72, 76 or 80, respectively.

No study drug will be administered or injected at the final visit.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have a Discontinuation Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing AEs. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

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

The study is designed to enroll approximately 740 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. Study enrollment will be closed prior to reaching 740 subjects should a sufficient number of subjects fulfill remission criteria and be available for randomization at the end of Period 1 prior to full enrollment.

5.2 Selection of Study Population

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Subject age ≥ 18 years.

2. Subject with nr-axSpA fulfilling the Assessment of Spondyloarthritis International Society (ASAS) axial SpA classification criteria (see Appendix C and Appendix D), but not fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis (see Appendix H).
3. Subject has had an inadequate response to at least 2 NSAIDs over a 4-week period in total at maximum recommended or tolerated doses, or subject has an intolerance to or a contraindication for NSAIDs as defined by the Investigator.
4. Subject with objective evidence of active inflammation in the SI joints or spine on MRI or elevated high sensitivity C-reactive protein (hs-CRP) at screening (elevated hs-CRP is defined as any level greater than the upper limit of normal for the lab).
5. Subject is a candidate for anti-TNF therapy based on the investigator's opinion.
6. Subjects must have baseline disease activity as defined by having an ASDAS $\geq$ 2.100 (note, sites will need to use the Screening Visit hs-CRP to calculate ASDAS at Screening and Baseline Visits with the remainder of parameters visit-specific), BASDAI $\geq$ 4 and Patient's Assessment of Total Back Pain score $\geq$ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits (see Appendix E, Appendix F and Appendix G, respectively).
7. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. The results of the serum pregnancy test performed during the Screening Period and urine pregnancy test performed at the Baseline Visit must be negative.

   Examples of approved methods of birth control include the following:

   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
   - Hormonal contraceptives for 90 days prior to study drug administration;
   - A vasectomized partner.

8. 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, CXR, and a 12-lead ECG performed at Screening;
9. Subject has a negative TB Screening Assessment. If the subject has evidence of a latent TB infection; the subject must initiate and complete at least the first 2 weeks (or per local guidelines, whichever is longer) of the prescribed TB prophylaxis or have documented completion of a course of TB prophylaxis, prior to Baseline (see Section 5.3.1.1).
10. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
11. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Rationale for the Inclusion Criteria

Inclusion Criteria	Rationale
1 – 9	To select the appropriate subject population for this study.
10	To increase subject compliance potential.
11	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. Subject fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis at or prior to the Screening Visit (see Appendix H).
2. 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.

3. Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (i.e., natalizumab [Tysabri®], rituximab [Rituxan®], or efalizumab [Raptiva®]).
4. If entering the study on concomitant DMARDs, subject not on stable dose of MTX (≤ 25 mg per week) and/or SSZ (≤ 3 g per day) and/or hydroxychloroquine (≤ 400 mg per day) for 28 days prior to the Baseline Visit. All other oral DMARDs, with the exception of azathioprine or mercaptopurine (6-MP), are prohibited within 28 days prior to the Baseline Visit.
5. If entering the study on concomitant azathioprine (AZA) or 6-MP, subject not on stable dose (AZA ≤ 150 mg per day or 6-MP ≤ 75 mg per day) for 28 days prior to the Baseline Visit or is on AZA or 6-MP and another concomitant immunosuppressive drug at study entry.
6. If entering the study on concomitant NSAIDs, tramadol, and/or non-opioid analgesics, subject not on stable doses for 14 days prior to the Baseline Visit.
7. Subject on opioid analgesics or use of marijuana within 14 days prior to the Baseline Visit.
8. If entering the study on concomitant oral corticosteroids, subject not on stable dose of prednisone (≤ 10 mg per day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
9. Subject has received cyclosporine or other second line anti-rheumatic therapy (except MTX, SSZ, hydroxychloroquine, AZA or 6-MP) within 28 days prior to the Baseline Visit.
10. Subject has been treated with intramuscular, intra-articular joint injection(s) or spinal/paraspinal injection(s) of corticosteroids in the preceding 28 days prior to the Baseline Visit.
11. 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.

12. Subject with extra-articular manifestations (e.g., inflammatory bowel disease, psoriasis, uveitis, etc.) that are not clinically stable for at least 30 days prior to study entry.

13. Subject has a history of fibromyalgia or inflammatory arthritis of a different etiology other than SpA (e.g., rheumatoid arthritis, gout, systemic lupus erythematosus, polyarticular or systemic juvenile idiopathic arthritis).

14. 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.

15. Known hypersensitivity to adalimumab or its excipients as stated in the label (Table 3).

16. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.

17. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).

18. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.

19. Hepatitis B: HBs Ag positive (+) or detected sensitivity on the HBV-DNA PCR qualitative test for HBc Ab/HBs Ab positive subjects (see Section 5.3.1.1).

20. Chronic recurring infections or active TB.

21. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.

22. 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.
23. Positive pregnancy test at Screening or Baseline.
24. Female subjects who are breast-feeding or considering becoming pregnant during the study.
25. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
26. History of clinically significant drug or alcohol abuse in the last 12 months.
27. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

The Investigator should contact the AbbVie Medical Monitor identified in Section 6.5 if there are any questions regarding inclusion and exclusion criteria and subject eligibility.

Rationale for the Exclusion Criteria

Exclusion Criteria	Rationale
1	To select the appropriate subject population in the study.
2–25, 27	To avoid medical conditions, medications or procedures that may compromise subject safety and the ability to make causality assessments relative to adalimumab.
26	To increase subject compliance potential.

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.

The AbbVie study-designated physician identified in Section 6.5 should be contacted if there are any questions regarding concomitant or prior therapies.

In addition for patients age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, 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 below prior and concomitant medication categories 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
- antineoplastics
- other

5.2.3.1 Prior Therapy

All prior drug therapies for nr-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

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

The subject may not initiate any therapies for nr-axSpA treatment during the study other than non-drug therapy, e.g., physiotherapy and hydrotherapy, or as outlined below. All non-drug therapies administered to a subject during the study should be recorded in the eCRF as a concomitant medication.

Subjects may continue on stable doses of MTX, SSZ, hydroxychloroquine, AZA, 6-MP, prednisone and/or NSAIDs provided the stability requirements noted in Section 5.2.2 are met. All current DMARDs, corticosteroids, NSAIDs and analgesics specifically administered for nr-axSpA will be captured on the Concomitant Medication eCRF. Doses of these concomitant medications must remain stable throughout study participation (except as medically required due to an AE). Dose adjustments or induction of treatment with these agents based on the investigator's medical judgment is only permitted after 12 weeks of rescue therapy with OL adalimumab in subjects who meet flare criteria. All dose adjustments must be recorded in the eCRF. In addition, doses must be within the acceptable limits below:

- MTX (≤ 25 mg per week)
- SSZ (≤ 3 g per day)
- Hydroxychloroquine (≤ 400 mg per day)
- AZA (≤ 150 mg per day) or 6-MP (≤ 75 mg per day)

Subjects on stable doses of analgesic(s) may be allowed to continue during the study. However, opioid analgesics (except for tramadol) are prohibited throughout the study.

For patients who take analgesics on an as needed basis, analgesics must be discontinued for at least 24 hours prior to a study visit.

One intra-articular corticosteroid injection for a peripheral joint will be allowed from Baseline to Week 28 and one after 12 weeks of rescue therapy. Once a joint is injected it will be considered not evaluable/assessable ("NA") during the 28 days following injection. No spinal, para-spinal or SI joint injections are allowed during the study.

5.2.3.3 Prohibited Therapy

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 (Note: Consideration for inclusion of subjects who have used biologic therapy for a non-SpA indication will be considered on a case by case basis if discussed with the AbbVie Medical Monitor):
  - Etanercept (Enbrel®);
  - Infliximab (Remicade®);
  - Abatacept (Orencia®);
  - Anakinra (Kineret®);
  - Rituximab (Rituxan®);
  - Natalizumab (Tysabri®);
  - Tocilizumab (Actemra®);
  - Efalizumab (Raptiva®);
  - Golimumab (Simponi®);
  - Certolizumab (Cimzia®);
  - Ustekinumab (Stelara®);
  - Belimumab (Benlysta®)
- Live vaccines (during the study and for 70 days after the last dose of study drug).
- Rifampin/Pyrazinamide combination.
- All oral DMARDs other than MTX, SSZ, AZA, 6-MP or hydroxychloroquine.

- Opioid analgesics (other than tramadol) or marijuana, except as medically indicated for an AE.
- Any investigational drug of chemical or biologic nature.

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

5.2.3.4 Rescue Therapy

Subjects who flare in Period 2 (40-week, double-blind period) will be allowed rescue therapy. Flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.100. Rescue therapy will consist of OL adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. For subjects who meet flare criteria during Period 2 and start rescue therapy with OL adalimumab, further calculation of ASDAS is not required. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

After 12 weeks of rescue therapy with OL adalimumab eow, initiation of or change in a subject's concomitant medications for SpA including doses of DMARDs, corticosteroids, NSAIDs, and analgesics are permitted based on the investigator's medical judgment.

5.3 Efficacy, Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Subjects will be allowed a visit window of ±7 days for all study visits (with the exception of the Baseline Visit as there is a maximum of 42 days screening window).

If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline Visit).

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

Table 1. Study Activities

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Informed Consent	X																									
Inclusion/ Exclusion Criteria	X	X[b]																								
Medical/ Surgical History	X	X[b]																								
Vital Signs/ Weight/ Height[c]	X	X	X	X	X	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	X		X	X	X	X	
Physical Exam	X	X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
12-Lead ECG[d]	X[e]																									
Chest X-Ray[d]	X[e]															X[f]										
AP Pelvis X-Ray	X[e]																									

Table 1. Study Activities (Continued)

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
TB Screening (PPD Skin Test OR IGRA)	X[e]															X[f]										
Pregnancy Test	X[g]	X[h]						X[h,v]	X[h,v]	X[h,v]										X[h]		X[h,v]	X[h,v]	X[h]	X[h]	
Chemistry and Hematology	X	X[i]		X	X	X	X	X	X	X		X		X		X				X		X[v]	X[v]	X	X	
Urinalysis[j]	X	X[i]				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
HLA-B27	X[e]																									
Antinuclear Antibody (ANA)/ reflex Anti-dsDNA antibody	X[e]																									
HBV Screening	X																									
hs-CRP	X	X[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
HIV	X[k]																									

Table 1. Study Activities (Continued)

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Biomarkers[l]		X						X[v]	X[v]	X		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
Serum ADA Concentration[l]		X				X		X[v]	X[v]	X		X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
Anti-ADA antibody (AAA)[l]		X				X		X[v]	X[v]	X		X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
PG Sample		X[m]																								
MRI of the Spine and SI Joints	X[e]							X[n]	X[n]	X[n]																
TJC/SJC		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
$BASMI_{lin}$		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
MASES		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	

Table 1. Study Activities (Continued)

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Plantar Fascia Enthesitis		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
Dactylitis		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
BASFI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Physician's Global Assessment of Disease Activity NRS		X	X	X	X	X	X	X	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	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	X	X	X	X		X	X	X	X	
Patient's Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	

Table 1. Study Activities (Continued)

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Patient's Global Assessment of Pain NRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
HAQ-S		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
SF-36V2 Health Survey		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
WPAI- axial SpA		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
EQ-5D		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
Prior and Concomitant Therapy Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Monitor AE	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X[p]
ASDAS Calculation	X	X						X[q]	X[q]	X[q]		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]						
Enrollment		X																								
Randomization										X[q]																

Table 1. Study Activities (Continued)

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Dispense Study Drug		X		X	X	X	X	X	X	X[q]	X	X	X	X	X	X	X	X	X	X[s]		X[s]	X[s]			
Admin of Study Drug[t]		X	X	X	X	X			X																	
Optional Blood Sample Collection Sub-Study		X						X[y]	X[y]	X		X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]						

Ada = Adalimumab; BL = Baseline; D = Day(s); Disc Visit = Discontinuation Visit; SCR = Screening; RT = Rescue Therapy; PF = Post Flare; F/U = Follow-up

a. Baseline Visit is defined as Day 1, the day of first study drug administration.

b. Medical History and Inclusion/Exclusion Criteria must be confirmed by the Investigator prior to enrollment to verify subject eligibility.

c. Height will be measured at Screening Visit only.

d. Subject can have a repeat CXR and/or ECG at any time during the study only if in the opinion of the investigator, clinically significant AEs develop that warrant a repeat exam.

e. These procedures will not be required if the subject had a previous normal CXR, normal ECG or negative PPD 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 or AP Pelvis x-ray will also not be required if the subject had a previous test within 30 days and 1 year (365 days) of Screening, respectively. Any documentation of past positive PPD results may be acceptable; however, negative PPD test done more than 90 days prior to the Screening visit will need to be repeated. If the subject has a positive PPD test or IGRA test, has had a past ulcerative reaction to PPD placement and/or a CXR consistent with prior TB exposure, the subject will be required to initiate and complete at least the first 2 weeks (or per local guidelines, whichever is longer) of the prescribed TB prophylaxis, or have documented completion of a full course of TB prophylaxis prior to Baseline (Section 5.3.1.1). There is no need to redraw the HLA-B27 or ANA once the results are available from the central laboratory chosen for this study.

Table 1. Study Activities (Continued)

f. An annual PPD/IGRA test will be required for those subjects with a negative TB test at Screening. If the annual PPD/IGRA test is positive, a CXR must be performed, the investigator must contact the study designated physician to review the individual data and agree on a decision whether or not additional evaluation is needed.

g. All females of childbearing potential will have a serum pregnancy test at Screening that is performed at the central laboratory.

h. All females of childbearing potential will have a urine pregnancy test performed at Baseline prior to study enrollment and at study discontinuation/completion. The urine pregnancy kit supplies will be provided to the sites via the central laboratory (where allowed by local guidelines). Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study.

i. Laboratory assessments (chemistry, hematology, hs-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 by the central laboratory 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. If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to HIV, and document that the test has been performed. The testing is to be done at a local laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

l. Flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.100. Subjects that flare during the double-blind period (Period 2) will need the following assessments during the visit that flare was determined as well as 12 weeks following the determination of the flare: biomarkers (refer to Section 5.3.1.1 for further information), serum adalimumab and AAA (refer to Section 5.3.2 for further information). These assessments are in addition to the regularly scheduled assessments outlined in the table above.

m. The pharmacogenic (PG) sample is optional. A separate PG consent form must be signed prior to sample collection. The PG sample is ideally collected at Baseline, but may be collected at any time throughout the study.

n. Site staff should schedule the Week 28 MRI during the Baseline visit, if possible. For subjects that are discontinued due to not fulfilling the ASDAS remission criteria at Weeks 20 or 24, the site should attempt to reschedule the MRI within 2 weeks (14 days) of the discontinuation visit. If the MRI cannot be rescheduled, the Week 28 MRI will be considered missed.

o. SAEs will be collected starting from time of signing informed consent; non-serious AEs will be collected starting from the 1st study drug dose. Any AE that occurs between Screening and Baseline should be captured as medical history.

p. Site personnel will contact all subjects 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.

Table 1. Study Activities (Continued)

q. Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued. At Week 24, calculation of the Week 20 ASDAS will be done using the Week 20 visit parameters including the Week 20 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued. At Week 28, calculation of the Week 24 ASDAS will be done using the Week 24 parameters including the Week 24 hs-CRP; the Week 28 ASDAS will be done using Week 28 parameters and the Week 24 hs-CRP (as the Week 28 results will not be available). If any of these time points do not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued. For hs-CRP elevations secondary to AEs or using a previous hs-CRP, please refer to Section 5.1 or ASDAS Calculation in Section 5.3.1.1.

r. Beginning at Week 36, ASDAS will be calculated via IVRS/IWRS for the current and previous study visit to determine fulfillment of flare criteria. Assessments from the current and previous study visit will be used for the calculation except for the hs-CRP which will be based on the results from the previous study visit's blood draw for both calculations. For subjects who meet flare criteria during Period 2 and start rescue therapy with OL adalimumab, further calculation of ASDAS is not required. For any subject missing 2 consecutive visits within the double-blind period (Period 2) the site must contact the AbbVie Medical Monitor for discussion regarding the subject's continued participation in the study.

s. Subjects would only receive study drug at Weeks 68, 72 or 76, if they flared at Week 56, 60 or 64 respectively.

t. Study drug will be administered in the Investigator's office at Baseline, Week 2, 4, 8, 12, and Week 24 to ensure proper technique.

u. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

v. These procedures should only be performed if the visit is the subject's last visit due to not meeting ASDAS remission criteria (Weeks 20, 24 or 28) or due to a flare and has received 12 weeks of rescue therapy (Weeks 72 or 76).

w. If subject meets flare criteria, these assessments are required 12 weeks post flare in addition to assessments for the scheduled visit when the flare was identified. If any of these procedures are already collected at the regularly scheduled visit, there is no need to obtain these procedures twice.

x. Subjects who prematurely discontinue the study should complete the procedures outlined for the Discontinuation Visit as soon as possible after the last dose of study drug and preferably prior to the administration of new therapies. No Discontinuation Visit procedures will be required for those subjects that complete the Week 68 visit (or Weeks 72, 76 or 80 for those subjects who flare at Weeks 60, 64 or 68, respectively).

y. Optional Blood Sample Collection Sub-Study only: use a separate sub-study central lab kit. Samples will be collected at Week 28 or at Weeks 20 or 24 only if the visit is the subject's last visit. (Optional Blood Sample Collection Sub-Study samples are in addition to the regularly scheduled assessments outlined in the table above.)

z. Optional Blood Sample Collection Sub-Study only: use a separate sub-study central lab kit. In subjects who meet flare criteria during Weeks 36 – 68, samples will be collected only once at time of flare. Flare is defined as 2 consecutive study visits with ASDAS ≥ 2.100. (Optional Blood Sample Collection Sub-Study samples are in addition to the regularly scheduled assessments outlined in the Table above.)

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 6.0). All study data will be recorded on the appropriate eCRFs.

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 procedures are undertaken, or before any medications are withheld from the subject in order to participate in this study. An additional consent is required for those subjects who agree to participate in the optional pharmacogenetic portion of the study. Details about how informed consent will be obtained and documented are provided in Section 9.3.

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 drug 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 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 drug administration and updated as necessary throughout the study on the eCRF.

Vital Signs, Weight and Height

Vital sign 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

During the Screening period, detailed medical history of anterior uveitis, as confirmed by an ophthalmologist, will be documented (if applicable). It should include the date of initial diagnosis, number 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 patient, self-reported.

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 dosing should be recorded as adverse events.

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. 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 Medical Monitor 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)

All subjects will undergo a standard CXR (PA and lateral views) at the Screening Visit 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 Screening, 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.

Anteroposterior Pelvis X-ray

Anteroposterior (AP) pelvis x-ray to evaluate the SI joints will be obtained during the Screening Period. The AP pelvis x-ray will not be required if the subject had a previous AP pelvis x-ray (film with required report results must be available to the site) within 1 year (365 days) of Screening. The Screening Visit AP pelvis x-ray should be performed prior to the MRI, to rule out radiographic evidence for AS (based on the modified New York criteria – Appendix H) which would exclude enrollment of this subject *(Note: if the Central Imaging vendor confirms a positive AP pelvic x-ray for AS and the MRI has not been performed, the MRI should be cancelled as the subject would be considered a screen failure).*

The AP Pelvis x-ray will be assessed locally for sacroiliitis grade to determine the presence (positive) or absence (negative) of sacroiliitis (presence = sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3-4 unilaterally) by a qualified rheumatologist or radiologist prior to sending the AP Pelvis x-ray to the central imaging vendor for assessment.

Grade	Definition
Grade 0	Normal
Grade 1	Suspicious changes
Grade 2	Minimum abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width)
Grade 3	Unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis)
Grade 4	Severe abnormality (total ankylosis)

Only x-rays negative for sacroiliitis should be sent to BioClinica (negative = bilateral grade ≤ 1 or if grade 2, only present unilaterally). If the central reader's assessment does not match the local reader's assessment (AS versus non-AS), a second central reader (adjudicator), will assess the pelvis x-ray. If adjudication is necessary, the second central reader's (adjudicator's) interpretation will be the final assessment sent to the site. A subject cannot be enrolled until the AP pelvis x-ray has been centrally assessed for the presence/absence of sacroiliitis and the report is available to the site. The imaging vendor will complete an imaging worksheet and return an eligibility notification report to the site within 48 hours of imaging vendor's receipt of the films (or within 96 hours if adjudication is necessary), not including BioClinica holidays or weekends. The investigator will be required to review, sign and date the eligibility notification report prior to the subject being enrolled.

Note: The AP Pelvis x-ray will only be assessed by the imaging vendor for sacroiliitis, and will not be assessed for any other clinically significant findings that may impact a subject's health.

Images will be sent to the central imaging vendor designated by the Sponsor. Procedures for performing and shipping the AP pelvis x-rays will be provided in a separate manual. The central imaging vendor chosen for this study is:

BioClinica, Inc.
826 Newtown Yardley Road
Newtown, PA 18940

TB Screening

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or an IGRA test must be performed locally during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

If a subject had a negative PPD or IGRA test within 90 days prior to Screening, 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.

For the PPD test:

The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours (or according to manufacturer's guide) after placement when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The induration must be recorded in mm not as positive or negative. The absence of induration should be recorded as "0 mm," not "negative." *(If required by specific counties a two-step test may be performed per local guidelines. The result of the second test should be recorded. An induration of 5 mm or greater will be considered as PPD positive.)*

Subjects who have had an ulcerating reaction to a PPD skin test in the past should not be re-exposed and should not be tested at Screening but will be considered PPD positive.

If there are sites where the accepted testing materials are not available an alternative may be substituted, but the method must be submitted 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 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. 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 PPD or 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 the first 2 weeks (or per local guidelines, whichever is longer) of the prescribed course of Center for Disease Control (CDC) recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy.

Subjects with a prior history of latent TB that have a documented completion of the 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 the first 2 weeks of the prescribed TB prophylaxis (or per local guidelines, whichever is longer) 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.

In the event both a PPD test and an IGRA test are performed, the result of the IGRA test will supersede the result of the PPD test. If the IGRA test is indeterminate, the site should repeat the test with another blood sample or perform a PPD test. 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 sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or reside or work in TB

endemic locations. The information obtained by the pulmonologist must be documented in the patient's source note, dated and signed by the pulmonologist.

- A pulmonologist must review the results of the PPD skin test or the IGRA test and the chest x-ray and has to give his/her opinion about the eligibility of each patient to be enrolled to the study. This opinion must be documented in writing in the patient's source documents.
- All patients with a positive PPD or IGRA test need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie Medical Monitor and all such patients need to receive prophylaxis for latent TB. Under no circumstances can a patient with a positive PPD or IGRA test result and no prior history of treatment for active or latent TB be allowed into this trial.

For subjects with a negative TB test at Screening, either an annual PPD or IGRA test will be required for any subject participating in the trial at Week 52 (Table 1). If the annual TB screen is positive (PPD is positive or the IGRA test is positive), a CXR will be required for evaluation of active TB. For any subject with a positive annual TB screen the site should contact the AbbVie Medical Monitor for further discussion. Subjects found to have latent TB, will be required to start a course of CDC recommended prophylaxis or prophylaxis per local guidelines as soon as possible. Subjects found to have active TB must discontinue study drug and receive CDC recommended or local guideline recommended treatment. Any positive TB screen after the patient has started the study, should be reported as an AE.

An annual TB screen with PPD or IGRA testing will not be required for subjects who have been treated for latent or active TB or have had a positive TB test (PPD or IGRA) at any time (prior to the study, Screening, annual evaluation, or testing performed at any time point during the study). For such subjects, annual evaluation by a physician for clinical signs/symptoms of active TB (including a directed TB history and physical exam including lungs, lymph nodes and skin) or newly identified TB risk factors will be required for any subject participating in the trial at Week 52. 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 (sent and analyzed at the central lab). 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 by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities.

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

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.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. 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. 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.

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

Urine samples will be obtained for macroscopic urinalysis (dipstick done at the central 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.

The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug. The certified laboratory chosen for this study is:

Covance CLS
8211 SciCor Drive
Indianapolis, IN 46214-2985 USA

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity pH Protein Glucose Ketones Blood Nitrite **Others** Pregnancy test HbsAg HBsAb HBcAb HBV DNA PCR reflex only hs-CRP HLA-B27 ANA/reflex Anti-dsDNA antibody

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, once results are available from the central laboratory chosen for this study repeat HLA-B27 testing is not required.

ANA

Testing for ANA will be performed on specimens collected during the Screening visit. For subjects that may need to be rescreened, once results are available from the central laboratory chosen for this study repeat ANA testing is not required.

Hepatitis B Testing

All subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening. A positive result for the Hepatitis B surface antigen (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). If test results are positive for HBc Ab or HBs Ab, HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

High Sensitivity C-reactive Protein (hs-CRP) Test

Testing for hs-CRP will be performed on specimens collected at the designated study visits listed in Table 1. The hs-CRP will be used as a parameter for the Ankylosing Spondylitis Disease Activity Score (ASDAS) calculation. See the ASDAS Calculation section below for more details on which hs-CRP to use during the ASDAS calculations.

Following Week 36, when entering the current visit as well as the prior visit parameters to calculate ASDAS for flare, the site should use the prior hs-CRP results for both calculations. For example, when entering the parameters for the Week 32 and Week 36 ASDAS calculation during the Week 36 Visit, the site should use the Week 32 Visit hs-CRP.

HIV Testing

If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to the HIV at Screening, and document that the test has been performed. The testing is to be done at a local laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing, and will not be made aware of any positive result.

Biomarkers

Samples will be obtained for biomarkers at the designated study visits in Table 1 and described in more detail under Section 5.3.2.1. The final set of biomarkers to be analyzed may include the following:

- Dickkopf-1 (DKK-1)
- Sclerostin
- Bone Morphogenetic Protein – 2 (BMP-2)

- Bone Morphogenetic Protein – 7 (BMP-7)

The final selection of biomarkers for analysis will be based on both insights gained in the sub-study and available scientific knowledge at study completion.

At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research. Samples will be stored frozen for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug, in terms of tolerability and safety. These samples may also be used for the development of diagnostic tests related to adalimumab (or drugs of this class). AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for no longer than 5 years after completion of the study defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

Biomarker analyses are considered exploratory. Results for the primary biomarker analyses from the overall study and sub-study will be reported in a separate biomarker study report. The primary biomarker analyses do not preclude future analyses which are not within the scope of this study protocol and will therefore not be included in the separate biomarker study report.

Serum Adalimumab Concentrations

Samples will be obtained for serum adalimumab concentrations at the designated study visits in Table 1 and described in more detail under Section 5.3.2.1.

Anti-Adalimumab Antibodies

Samples will be obtained for anti-adalimumab antibodies at the designated study visits in Table 1 and described in more detail under Section 5.3.2.1.

Pharmacogenetic Sample

Samples will be obtained for pharmacogenetic analysis at the designated study visits in Table 1 and described in more detail under Section 5.3.2.1.

MRI of the Spine and Sacroiliac Joints

All subjects will have an MRI evaluation of the SI joints as well as the cervical, thoracic and lumbar regions of the spine during the Screening Period and Week 28 Visit. 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 30 days of the Screening Visit.

(Note: if the Central Imaging vendor confirms a positive AP pelvic x-ray for AS and the MRI has not been performed, the MRI should be cancelled as the subject would be considered a screen failure).

Subjects cannot be enrolled until the Screening MRI image has been centrally read for the presence/absence of active inflammation in the SI joints and spine and the report is available to the site. The imaging vendor will complete an imaging worksheet and return an eligibility notification report to the site within 48 hours of imaging vendor's receipt of the films. The investigator will be required to review, sign and date the eligibility notification report prior to the subject being enrolled.

Note: The MRI will only be assessed by the imaging vendor for bone marrow edema, and will not be assessed for any other clinically significant findings that may impact a subject's health.

Images will be sent to the central imaging vendor designated by the Sponsor. Procedures for performing and shipping the MRIs are provided in a separate manual. The central imaging vendor chosen for this study is:

BioClinica, Inc.
826 Newtown Yardley Road
Newtown, PA 18940

Note: It is expected all subjects will have a Week 28 MRI, even those subjects that are discontinued at Weeks 20, 24 or 28 due to lack of meeting the ASDAS remission criteria. Site staff should schedule the Week 28 MRI during the Baseline visit, if possible. For subjects that are discontinued for any reason at Weeks 20, 24 or 28, the site should attempt to reschedule the MRI within 2 weeks (14 days) of the discontinuation visit. If the MRI cannot be rescheduled within 14 days of the discontinuation visit, the Week 28 MRI will be considered missed.

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 I).

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.

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 I).

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 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 ($BASMI_{lin}$)

The $BASMI_{lin}$ will be conducted at the designated study visits in Table 1 to evaluate spinal mobility in a subject (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.

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 K).

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

Plantar Fascia Enthesitis

Evaluation for plantar fascia enthesitis will be conducted at the designated study visits in Table 1 to assess the presence or absence of plantar fascia enthesitis on the right and left feet.

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

Dactylitis

This evaluation 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 L). This assessment should be completed prior to any other study related procedures being performed.

Numerical Rating Scales (NRS)

Numerical Rating Scales will be used to assess the physician 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 M). 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.
- Patient's assessment of nocturnal back pain (within the last week)
  - The patient's assessment of nocturnal back pain (Appendix N)
- Patient's assessment of total back pain (within the last week)

  - The patient's assessment of total back pain (Appendix G)
- Patient's global assessment of disease activity (within last week)
  - The patient's overall assessment of disease activity within the last week (Appendix O)
- Patient's global assessment of pain (within last week)
  - The patient's assessment of pain (Appendix P)

These assessments should be completed prior to any other study related procedures being performed in the order outlined on Table 1.

Health Outcomes Questionnaires

Subjects will complete the following questionnaires: Health Assessment Questionnaire modified for the Spondyloarthropathies (HAQ-S) (Appendix Q), Short Form-36 Health Status Survey Version 2 (SF-36v2) (Appendix R), Work Productivity and Activity Impairment Questionnaire – Specific Health Problem Questionnaire (WPAI-axial SpA) (Appendix S), and the European Quality of Life – 5 Dimension Questionnaire (EQ-5D) (Appendix T). The HAQ-S will assess the physical function and health related quality of life of each subject. The SF-36v2 and EQ-5D will assess the subject's view of their health. The WPAI-axial SpA 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 nr-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

The ASDAS will be calculated for the visits outlined in Table 1. During the Screening visit, the hs-CRP will be drawn and sent to the central lab. *Note: the ASDAS calculation cannot be entered into IVRS/IWRS until the hs-CRP result is returned from the central lab. If the subject does not meet the criteria of an ASDAS ≥ 2.100 at screening, the subject would be considered a screen failure and all other screening procedures should be cancelled.* During the Baseline Visit, the ASDAS parameters will be entered in IVRS/IWRS to determine if a subject met the ASDAS entry criteria. The site will need to use the Screening hs-CRP for both the Screening and Baseline Visits and visit-specific information for the remaining parameters.

The ASDAS calculation in Period 1 (OL) will be done at Weeks 20, 24 and 28 (prior to randomization). All ASDAS visit parameters listed in Appendix E should be used from each study visit (with the possible exception of hs-CRP as described below).

At Week 20, sites will enter the ASDAS parameters into IVRS/IWRS using the IVRS/IWRS worksheets provided separately. At Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

At Week 24, sites will enter the ASDAS parameters into IVRS/IWRS using the IVRS/IWRS worksheets provided separately. At Week 24, calculation of the Week 20 ASDAS will be done using the Week 20 visit parameters including the Week 20 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

At Week 28, sites will enter the ASDAS parameters into IVRS/IWRS using the IVRS/IWRS worksheets provided separately. At Week 28, calculation of the Week 24 ASDAS will be done using the Weeks 24 parameters including the Week 24 hs-CRP; the Week 28 ASDAS will be done using Week 28 parameters and the Week 24 hs-CRP (as

the Week 28 results will not be available). If any of these time points do not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Subjects may be discontinued as early as Week 20 if they do not meet the ASDAS remission criteria using the Week 16 parameters.

Due to the importance of the Week 16, 20 and 24 visits, two or more missed visits during this time must be discussed with the AbbVie Medical Monitor prior to randomization. If a subject misses a single visit at Week 16, 20, or 24 the site will need to use the ASDAS parameters from the visit immediately prior to the missed visit. If a subject misses the Week 28 visit, the subject must be discontinued.

Subjects meeting the remission criteria at Weeks 16, 20, 24 and 28 will be randomized into Period 2. Subjects not meeting the ASDAS Inactive Disease at Weeks 16, 20, 24 or 28 will be discontinued.

Subjects who flare in Period 2 (40-week double-blind period) will be allowed rescue therapy. Starting at Week 36 through Week 68, subjects will be assessed for flare, defined as 2 consecutive visits with ASDAS ≥ 2.100. The hs-CRP from the prior visit will be used to calculate the ASDAS for both the prior visit and the current visit with the remainder of the ASDAS parameters visit-specific. If a subject misses a visit, the site will need to use the ASDAS parameters from the visit immediately prior to the missed visit in order to determine the 2 consecutive ASDAS for assessment of flare.

If a subject has an elevated hs-CRP which the investigator believes to be secondary to an AE and not due to nr-axSpA, sites may repeat the hs-CRP test prior to the subject's next scheduled visit following a discussion with the AbbVie Medical Monitor. The repeat hs-CRP results should be available to the site prior to the subject's next scheduled visit and will replace the visit-specific hs-CRP in the ASDAS calculation. Instances where AE-related hs-CRP elevation spans more than one study visit will be addressed on a case-by-case basis. *Note: the AE should be reported in EDC prior to discussion with the AbbVie Medical Monitor.*

Note: site will need to enter the ASDAS parameters used for calculation outlined in Appendix E into IVRS/IWRS. Source worksheets will be available for sites to use during the IVRS/IWRS entry. For subjects who meet flare criteria during Period 2 and start rescue therapy with OL adalimumab, further calculation of ASDAS is not required. *For any* subject missing 2 or more consecutive visits within the double-blind period (Period 2) the site must contact the AbbVie Medical Monitor for discussion regarding the subject's continued participation in the study.

Enrollment

Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will be enrolled into Period 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 3 digits represent the site number and the last 2 digits represents a sequential number. Site numbers will be assigned sequentially.

Randomization

During the Week 28 visit, subjects meeting ASDAS Inactive Disease (ASDAS < 1.300) at Weeks 16, 20, 24 and 28 will be randomized using IVRS/IWRS in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo. Subjects not meeting the ASDAS Inactive Disease at Weeks 16, 20, 24 or 28 will be discontinued.

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

Study drug will be administered in the Investigator's office at Baseline, Weeks 2, 4, 8, 12, and Week 24 to ensure proper technique and described in more detail under Section 5.5.

70-Day Follow-Up Call

All subjects 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 adalimumab 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 U). 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.

Optional Blood Sample Collection Sub-Study

An Optional Blood Sample Collection Sub-Study for future research (separate from the blood sample collection listed above) will be offered to approximately 10 sites based on interest, ongoing enrollment and clinical trial conduct. Samples will be obtained for the Optional Blood Sample Collection Sub-Study at up to three time points (baseline, remission/Week 28 [Weeks 20 or 24 if the subject's last visit], and at time of flare, if applicable). Timing of blood samples to be obtained are outlined in the designated study visits in Table 1 and described in more detail within the "Optional Blood Sample Collection Sub-Study Guidelines," which will be sent separately to the approved sub-study sites.

5.3.2 Drug Concentration, Pharmacogenic, and Biomarker Measurements

Blood samples for the pharmacokinetic (PK) measurement of serum adalimumab levels and anti-adalimumab antibody (AAA) concentrations will be taken at the following time points:

- Blood samples will be collected at Baseline, Weeks 12, 28, 36, 52, 68 or at the Discontinuation Visit.

- Subjects who flare during the double-blind period (Period 2) will have blood samples collected at the visit that flare was determined as well as 12 weeks following the time of determination of flare. Subjects who meet flare criteria at Weeks 36, 40, 44, 48, 52, 56, 60, 64 or 68 will have blood samples collected at Weeks 48, 52, 56, 60, 64, 68, 72, 76 or 80, respectively.

Blood samples for biomarker analysis will be collected at Baseline, Weeks 28, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit.

A blood sample for the optional PG analysis is ideally collected at Baseline, but may be collected at anytime throughout the study.

Sites approved for the Optional Blood Sample Collection Sub-Study should refer to the "Optional Blood Sample Collection Sub-Study Guidelines" for collection, handling/processing, storage and disposition of samples.

5.3.2.1 Collection of Samples for Analysis

Serum Adalimumab Concentration and AAA Analysis

Blood samples for serum adalimumab concentration and AAA will be collected by venipuncture into appropriately labeled 6 mL evacuated serum collection tubes without gel separator. The central laboratory will provide supplies for sample collection, processing, storage and shipment. Please refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipment.

The time that each blood sample is collected will be recorded to the nearest minute and entered into the appropriate eCRF.

Serum adalimumab concentration and AAA samples will be collected prior to dosing at the study visits specified in Table 1.

Biomarker Analysis

Blood samples for biomarker analysis will be collected by venipuncture into appropriately labeled 6 mL evacuated serum collection tubes without gel separator. The central laboratory will provide supplies for sample collection, processing, storage and shipment. Please refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipment.

At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research. Samples will be stored frozen for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug, in terms of tolerability and safety. These samples may also be used for the development of diagnostic tests related to adalimumab (or drugs of this class). AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for no longer than 5 years after completion of the study defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

The time that each blood sample is collected will be recorded to the nearest minute and entered into the appropriate eCRF.

Biomarker sample collection will be **prior to dosing** at the study visits specified in Table 1.

Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected during the Baseline visit *(the PG sample is ideally collected at Baseline, but may be collected at anytime throughout the study*) from each subject who consents to provide samples for pharmacogenetic analysis. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

The time that each blood sample is collected will be recorded to the nearest minute and entered into the appropriate eCRF.

5.3.2.2 Handling/Processing of Samples

The Adalimumab Concentrations, AAA, Biomarkers and PG samples will be handled/processed as outlined below. At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research. Subjects will be able to decline storing samples for possible future research during the consenting process discussed further in Section 9.3.

Serum Adalimumab Concentration and AAA Analysis

The blood will be allowed to clot for 30 minutes at room temperature and then centrifuged for approximately 10 minutes at 1100 to 1600 × g. The collected serum volume will be transferred using plastic pipettes and split equally into four screw-capped polypropylene tubes labeled with the study drug name, type of sample (serum [SRM]), the protocol number, the subject number, the time point sampling relative to dosing, PK or AAA (for adalimumab or anti-adalimumab antibody), split number (1 or 2) and then will be stored frozen at –20°C or colder and remain frozen until shipped *(note: sites should ship split 1 and split 2 separately to the central laboratory and Samples should be shipped to the central lab within 4 weeks of the draw date.)* Samples will be stored frozen at –70°C or colder once received at the central laboratory. Sites that do not have access to a –20°C or colder freezer must ship the serum samples with dry ice the same day they are collected.

Arrangements will be made with the central laboratory to ship samples to AbbVie for analysis. The frozen samples will be eligible for disposal per AbbVie's SOPs (where allowed by local guidelines).

Biomarker Analysis

The blood will be allowed to clot for 30 minutes at room temperature and then centrifuged for approximately 10 minutes at 1100 to 1600 × g. The collected serum volume will be

transferred using plastic pipettes and split equally into four (or five if a subject consents to the additional serum to be stored for possible future research) screw-capped polypropylene tubes labeled with the study drug name, type of sample (serum [SRM]), the protocol number, the subject number, the time point sampling relative to dosing, BM (for biomarker assay), aliquot number (1, 2, 3, 4 or 5 if applicable) and then will be stored frozen at –20°C or colder remain frozen until shipped. Samples should be shipped to the central lab within 4 weeks of the draw date. Samples will be stored frozen at –70°C or colder once received at the central laboratory. Sites that do not have access to a –20°C or colder freezer must ship the serum samples with dry ice the same day they are collected.

At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research. Samples will be stored frozen for future exploratory analysis of non-genetic biomarkers related to the subject's disease and/or response to study drug, in terms of tolerability and safety. These samples may also be used for the development of diagnostic tests related to adalimumab (or drugs of this class). Results of exploratory analyses, if any, will not be reported with the study summary. AbbVie will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained for no longer than 5 years after completion of the study defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

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

Pharmacogenetic Analysis

Whole blood will be collected by standard phlebotomy technique as described below.

- Collect approximately 4 mL of blood into an appropriately labeled ethylenediaminetetraacetic acid (EDTA) tube (lavender top).
- Immediately invert the collection tube 8-10 times to reduce the likelihood of clot formation.

- Store samples at –20°C or colder within 30 minutes of blood draw until shipped to the central laboratory on dry ice sufficient to last during transport.

Samples will be shipped frozen to the certified central laboratory for handling prior to shipment to AbbVie for DNA extraction and long-term storage.

The sample collection tubes will be labeled as "PG-DNA blood," with the drug number, protocol number, subject number, and study day (i.e., Baseline). AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on adalimumab (or drugs of this class) continues but no longer than 5 years defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

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

5.3.2.3 Disposition of Samples

The frozen blood samples will be packed in dry ice per the central laboratory instruction manual. Samples will be shipped pursuant to instructions from the central laboratory manual. An inventory of the samples included will accompany the package.

5.3.2.4 Measurement Methods

Serum concentrations of adalimumab and AAA will be determined using validated ligand binding methods under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

5.3.3.1 Primary Efficacy Variable

The primary efficacy variable is the proportion of subjects who do not experience a flare during Period 2 by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS $\geq$ 2.100.

5.3.3.2 Secondary Efficacy Variable(s)

Secondary efficacy variables include the following:

At 12 Weeks after Initiation of Rescue Therapy

- ASDAS Inactive Disease (ASDAS < 1.300)
- ASDAS Major Improvement (a change from baseline ≤ –2.000)
- ASDAS Clinically Important Improvement (a change from baseline ≤ –1.100)
- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
    - ASAS20 response: improvement of ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit)
        - Patient's Global Assessment – Represented by the PTGA-disease activity NRS score (0 to 10)
        - Pain – Represented by the patient's assessment of total back pain NRS score (0 to 10)
        - Function – Represented by the BASFI NRS score (0 to 10)
        - Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10])
    - ASAS40 response: improvement of ≥ 40% and absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in ≥ 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain
    - ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20
    - ASAS 5/6 response: 20% improvement from Baseline in 5 out of the following 6 domains: BASFI, patient's assessment of total back pain, PTGA-disease activity, inflammation (mean of items 5 and 6 of the BASDAI]) lateral lumbar flexion from BASMI, and hs-CRP
- Bath AS Disease Activity Index 50 (BASDAI50)

- Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

At Week 28 and Week 68

- ASDAS Inactive Disease
- ASDAS Major Improvement
- ASDAS Clinically Important Improvement
- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
- BASDAI50
- HAQ-S

At Week 68

- Time to flare defined as ASDAS $\geq$ 2.100 at 2 consecutive visits
- Time to partial flare defined as ASDAS $\geq$ 1.300 but < 2.100 at 2 consecutive visits
- Proportion of subjects who reach flare definition
- Proportion of subjects who reach partial flare definition

5.3.3.3 Other Efficacy Variables

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of Total back pain
- Bath AS Functional Index (BASFI)
- Inflammation/Morning Stiffness (mean of BASDAI questions 5 and 6)
- Bath AS Disease Activity Index (BASDAI)
- ASDAS
- hs-CRP
- Linear Bath AS Metrology Index ($BASMI_{lin}$)
- Swollen Joint Count (66 joints)

- Tender Joint Count (68 joints)
- MASES
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Pain
- Patient's Assessment of Nocturnal Back Pain
- Anterior Uveitis
- Short Form-36v2 Health Survey questionnaire
- EQ-5D
- WPAI-axial SpA
- SPARCC scores for MRI of the SI joint and spine
- Proportion of subjects who regain remission on rescue therapy
- Time to regain remission on rescue therapy

5.3.3.4 Exploratory Variables

Each subject will have blood drawn for Biomarkers at the following time points: Baseline, Weeks 28, 68, time of flare, 12 weeks following determination of flare, and last study visit. The final set of biomarkers to be analyzed may include the following:

- DKK-1
- Sclerostin
- BMP-2
- BMP-7

The final selection of biomarkers for analysis will be based on both insights gained in the sub-study and available scientific knowledge at study completion.

5.3.4 Pharmacogenetic Variables

Pharmacogenetic analysis is optional and requires subject's prior consent. DNA samples may be analyzed for genetic factors contributing to the subject's response to adalimumab, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to adalimumab or drugs of this class. The samples may also be used for the development of diagnostic tests related to adalimumab (or drugs of this class). The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.5 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: concomitant medication review, AE monitoring, vital signs, physical examination (if required) 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 for any reason, including an AE, safety concerns or failure to comply with the protocol.

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

- Clinically significant abnormal laboratory result(s) or AE(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.

- 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 noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor (see Section 5.2 and Section 6.5).
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- 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 Medical Monitor.
- Subject does not meet the criteria for remission at Weeks 16, 20, 24 and 28.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Discontinuation Visit must be completed within 2 weeks of the last dose of study drug, and preferably 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 the subject approximately 70 days after last dose 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. At 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.

Subjects who prematurely discontinue will not be replaced.

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. 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

Open-Label – Period 1

Starting on Day 1 through Week 26, subjects will be administered OL adalimumab 40 mg eow. Drug will be subcutaneously self-administered or administered by a qualified designee every other week at approximately the same time of day. The day of the first dose of study drug is designated as Day 1.

Subjects may be discontinued as early as Week 20 if they do not meet the ASDAS remission criteria using the Week 16 parameters. See the ASDAS Calculation in Section 5.3 for more details on which hs-CRP to use during the ASDAS calculations.

Subjects meeting ASDAS Inactive Disease at Week 16, 20, 24 and Week 28 will be randomized 1:1 to receive either blinded adalimumab 40 mg eow or matching placebo. Subject not meeting ASDAS Inactive Disease at Week 16, 20, 24 or Week 28 will be discontinued.

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 injection at the study visits at Baseline, Weeks 2, 4, 8, 12 and Week 24 to ensure proper injection technique (Appendix V). 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.

Double-Blind – Period 2

Starting at Week 28, subjects who are eligible for randomization into Period 2 will receive the first dose of blinded study drug (adalimumab 40 mg eow or placebo). The study drug will be provided as a sterile SC injection solution in 1 mL pre-filled syringes containing either adalimumab 40 mg/0.8 mL or matching placebo for adalimumab.

Rescue Therapy During Period 2

Starting at Week 36, subjects who meet the flare criteria (flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.100) will be given rescue therapy with open-label adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab 40 mg eow will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

5.5.2 Identity of Investigational Product(s)

The individual study drug information is presented in the following table:

Table 3. Identity of Investigational Products

Study Drug	Formulation	Manufacturer
Adalimumab	40 mg/0.8 mL 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	Abbott/AbbVie
Placebo for 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	Abbott/AbbVie

5.5.2.1 Packaging and Labeling

Open-label investigational product will contain 2 pre-filled syringes of adalimumab 40 mg/0.8 mL. Blinded investigational product will contain either 2 pre-filled syringes of adalimumab 40 mg/0.8 mL or 2 pre-filled syringes of placebo for adalimumab. The type and amount of kits dispensed will be managed by the IVRS/IWRS.

Each pre-filled syringe and carton will be labeled as required per country requirements. All blank spaces on the label will be completed by site staff prior to dispensing to the subject.

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/placebo pre-filled syringes are to be stored protected from light at 2°C to 8°C/36°F 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 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 GPRD or Abbott 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 local guidelines and a well-documented procedure is in place) or returned to AbbVie or third party drug destruction depot.

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 centrally enrolled (at the Baseline Visit) and randomized (at Week 28, if applicable) using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions as well as the appropriate URL for the IVRS/IWRS will be provided to each site.

IVRS/IWRS will be maintained by:

Perceptive Informatics
Windsor Corporate Park,
50 Millstone Road
Building 100, Suite 200
East Windsor, NJ 08520

Study drug will be administered at the study visits summarized in Table 1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.1.

If a subject should 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 W).

Doses not administered (e.g., not taken before the next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned to the study site full. 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

Period 1, defined as Baseline (Day 1) through Week 26 is OL.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the Investigator, study site personnel and the subject will remain blinded to each subject's treatment throughout the double-blinded period, Week 28 through Week 68 (Period 2) of the study. The IVRS/IWRS will provide access to blinded subject treatment information in case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie Medical Monitor (Section 6.5) prior to breaking the blind. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

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 administration of the study drug at in-office study visits 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 W) 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.

The Investigator or his/her designated representatives will make a photocopy of the subject doing diary at each visit.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature (except in the US, where it should be documented as cool to the touch), 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. For this study, unless otherwise prohibited locally, these records will be maintained electronically as part of the IVRS/IWRS system.

All empty IP boxes and used pre-filled syringes will be inventoried by the site and 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 diary 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 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. Unused medication will be returned by the CRA after drug accountability has been completed at 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 evaluate the efficacy and safety of adalimumab 40 mg eow versus placebo in maintaining remission in patients with nr-axSpA who achieve ASDAS Inactive Disease at the end of Period 1. Based on past clinical trials of adalimumab in AS and in nr-axSpA patients, 28 weeks of adalimumab treatment in Period 1 is expected to be sufficient to identify most subjects who will respond and achieve remission (ASDAS Inactive Disease) with this therapy. In Period 2, patients who achieve ASDAS Inactive Disease at Week 16, 20, 24 and Week 28 are randomized to receive either blinded adalimumab or placebo. The primary endpoint will be the proportion of subjects who do not experience a flare by Week 68. The proposed 40-week

duration of the double blind period is based on results of 2 prior trials that demonstrated the occurrence of disease flare in patients taken off anti TNF therapy. [14,15]

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 or designed to assess disease activity in subjects with nr-axSpA. Other than the biomarker and pharmacogenetic analysis which are 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 nr-axSpA who have a minimum level of disease activity at baseline (ASDAS ≥ 2.100, BASDAI ≥ 4, Patient's Assessment of Total Back Pain score ≥ 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), have had an inadequate response or intolerance to two or more NSAIDs or have an intolerance to, or a contraindication for NSAIDs, and who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study.

5.6.4 Selection of Doses in the Study

The recommended dose of adalimumab for adults with AS is 40 mg administered eow. Adalimumab is approved for the treatment of AS (in the US and EU) and approved for 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 Adverse Events

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 study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, 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 Definitions

6.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient 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 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 6.7 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.

6.1.2 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 SAE.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	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.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study 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).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the 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.

6.2 Adverse Event Severity

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

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

6.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug 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 study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration 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 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.

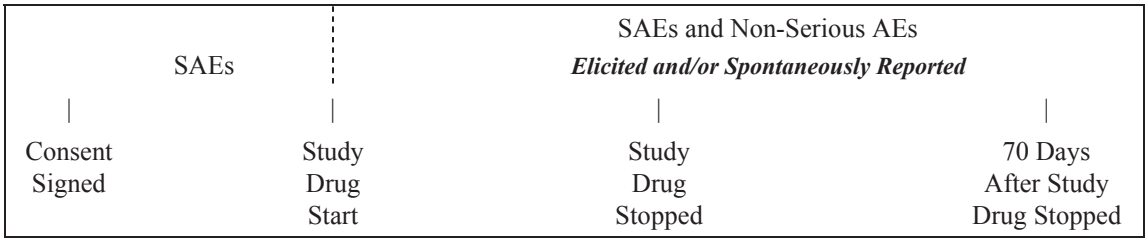
Adverse event information will be collected as shown in Figure 2.

Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects that are able to receive commercial adalimumab treatment after the end of study participation. These

subjects are not required to complete the 70-day follow-up and any new Adverse Events should be reported through the mechanism used for all post marketing adverse experiences.

There may be instances where a 70-day follow-up phone call occurs after the locking of the clinical database. In this situation, any Adverse Events reported to AbbVie from this 70-day follow-up phone call will be evaluated for inclusion in the clinical database. All SAEs or Adverse Events of Special Interest, as defined by AbbVie, reported during the 70-day follow-up phone call must be captured in the clinical database.

Figure 2. Adverse Event Collection



6.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the SAE or non-serious event of malignancy in subjects 30 years of age and younger into the electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® system or if RAVE is not operable should use the SAE Non-CRF paper forms and send them (email is the preferred route) to Clinical Pharmacovigilance within 24 hours of being made aware of the adverse event.

[redacted]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team Hotline
[redacted]

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

Primary Study Designated Physician:

[redacted]

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.

6.6 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 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 of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.7 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 treatments or if an infection meets the definition of "serious" (see Section 6.0 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 two weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

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 Independent Ethics Committee (IEC)/Independent Review

Board (IRB) regulatory authorities (as applicable) and their assigned CRO Clinical Monitor or the following AbbVie Clinical Members:

Primary Contact:	Alternate Contact:
[redacted]	

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.

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 and received at least one dose of double-blind study medication. 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 analysis of the primary efficacy variable may be conducted on the per protocol population, which consists of all ITT subjects who entered the double-blind period of the study and did not meet any major protocol violation during the OL and double-blind periods.

The safety population consists of all subjects who received at least one dose of study medication.

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. Primary analysis will not be adjusted for site effect since the subjects will be enrolled through a central randomization process.

All statistical comparisons for the primary efficacy endpoint will be performed at Week 68 (end of the placebo-controlled, i.e., double-blind period) and secondary efficacy endpoints will be performed at the time points specified in Section 5.3.3.2, unless otherwise stated.

An interim database lock is planned when all ongoing subjects have completed Week 28 (OL, Period 1) of the study. The OL study results (through Week 28) will be based on this database lock. Efficacy and safety data from this initial OL phase will be descriptive and presented for exploratory purposes only and no statistical comparison will be made. Therefore, no adjustment to the *P* value will be required for this interim reporting.

Data from the subsequent double-blind period will be reported at the completion of the study. 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 (the first dose of OL period) will be considered as the Baseline value. To account for any missing data for the primary efficacy endpoint (proportion of subjects who do not experience a flare by Week 68), a non-responder imputation approach will be used, i.e., subjects who discontinue during the double-blind period (Period 2) with missing flare data will be imputed as having a flare. The last observation carried forward (LOCF) rule will be used to impute missing continuous efficacy data at Week 68. That is, the subject's last non-missing value assessed in the study while receiving double-blind study drug will be used in the analysis. In addition, an analysis using only the observed or reported data will be performed as a sensitivity analysis for the primary endpoint. If deemed appropriate, hs-CRP values obtained during the Week 28 visit, will be used for the calculation of ASDAS inactive disease at the Week 28 visit for a sensitivity analysis since these values were not available at the time of randomization. Similarly, if deemed appropriate, hs-CRP values obtained at the second visit determining flare will be used for a sensitivity analysis since the visit-specific value was not available at the time of flare determination.

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, 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 Primary Efficacy Variable

8.1.4.1.1 Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study, which defined as having any 2 consecutive study visits with ASDAS ≥ 2.100, and the response rate observed in the group randomized to adalimumab 40 mg eow will be compared to that in the placebo group. The null hypothesis associated with this comparison states that there is no difference in response rates between the adalimumab and placebo groups; 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 $\alpha = 0.05$. Subjects who discontinue during the double-blind (Period 2) with missing flare data at Week 68 will be treated as non-responders according to "non-responder imputation" criterion.

8.1.4.1.2 Secondary Analysis of Primary Efficacy Endpoint

Secondary analyses of the primary endpoint will be conducted using observed case analysis for the proportion of subjects not experiencing a flare up to Week 68. The response rates will be compared using a two sided Pearson's chi square test with $\alpha = 0.05$.

8.1.4.2 Analyses of Secondary Efficacy Variables

Unless otherwise stated, all statistical comparisons of secondary efficacy variables will be conducted between the adalimumab group and placebo group at the 2-sided $\alpha = 0.05$ significance level.

A complete list of secondary efficacy variables is provided in Section 5.3.3.2. Discrete variables will be summarized using count and percentages and will be compared between adalimumab and placebo groups during the double-blind and rescue periods using Pearson's chi square test or Fisher's exact test (if ≥ 25% of the cells have expected counts less than 5).

Continuous efficacy variables will be summarized by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum). Change from Baseline in the continuous variables will be compared between adalimumab and placebo groups using an analysis of covariance method adjusting for the Baseline score. This will be done for both observed and LOCF imputed values.

Time to flare will be analyzed using a Cox proportional hazards model with treatment as a factor.

8.1.4.3 Other Exploratory Analyses

Analysis for other efficacy variables referenced in (Section 5.3.3.3) will be performed using similar methods to those described in Section 8.1.4.2.

8.1.5 Statistical Analyses of Safety

Safety analyses will be carried out using safety population, which includes all subjects that received at least one dose of study medication. Treatment-emergent, and pre- and post-treatment AEs will be summarized and reported. The rate of treatment-emergent AEs when starting OL adalimumab rescue therapy in subjects who have flared on placebo will be reported.

Treatment-emergent AEs are defined as AEs that begin either on or after the first dose of the study medication, and up to within 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. All treatment emergent AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®). The number and percent of subjects experiencing AEs will be tabulated by system organ class and preferred term. In addition, a summary of AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, 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 treated subjects, and compared between treatment groups during the double-blind period using a one way ANOVA. The last evaluation prior to the first dose of study drug 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 variable.

8.1.6 Pharmacokinetic Analyses

Adalimumab concentrations will be listed by individual and time point. For each scheduled time of measurement, summary statistics will be provided for the adalimumab serum concentration data by treatment group. If appropriate, concentration data may be combined with observed concentration data from previous Humira studies, and population pharmacokinetic analyses will be performed to estimate adalimumab apparent clearance and volume of distribution.

Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the Non-Linear Mixed Effect Modeling (NONMEM) software (Version V, or a higher version). A stepwise addition and deletion approach will be used to assess the impact of covariates on model parameters. Standard model evaluation approaches will be used to determine the performance of different models (e.g., objective function value comparison based on likelihood ratio test, visual predictive checks, magnitude of inter-subject and residual error etc.). The final model will be used to produce empirical Bayesian estimates of the pharmacokinetic parameters for each individual, using the post-hoc option in NONMEM. Individual pharmacokinetic parameters will be listed and summarized with appropriate statistical methods.

The percentage of subjects with AAA will be reported.

Additional pharmacokinetics/pharmacodynamic analyses may be conducted as appropriate.

8.1.7 Interim Analysis

No formal unblinded interim analysis is planned for this study that requires an adjustment to the *P* value. An interim analysis will be performed when all ongoing subjects have completed at least Week 28 of the study. The primary and secondary endpoints of the study from the double blind period will be reported at the completion of the study.

8.2 Determination of Sample Size

Assuming that 50% of subjects treated with adalimumab will not experience any flare up to Week 68, 120 subjects per arm are required for the double-blind period (Period 2) (with an adjustment for drop out rate of no more than 30%) is targeted to result in at least 90% power for detecting a 25% difference at Week 68 for the primary endpoint between adalimumab and placebo based on a two-sided test with significance level 0.05.

It is assumed that approximately 33% of the subjects enrolled into the OL Period (Period 1) would meet ASDAS Inactive Disease at Weeks 16, 20, 24 and Week 28, therefore, a total of approximately 740 subjects would be required to be enrolled in order to have sufficient number of subjects (i.e., 120 subjects per arm) for the double-blind period. Study enrollment will be closed prior to reaching 740 subjects should a sufficient number of subjects fulfill remission criteria and be available for randomization at the end of Period 1 prior to full enrollment.

8.3 Randomization Methods

Subjects who meet the remission criteria at Week 28 of the Open-Label Period will be randomized in a 1:1 ratio to receive either adalimumab 40 eow or matching placebo for 40 weeks.

9.0 Ethics

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

Good Clinical Practice (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.

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.

At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research. The storage of these biomarker samples for possible future research is optional and subjects' may decline at any time.

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 incentives for subjects and 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.

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent form, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The separate pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing it will not impact the subject's participation in the study.

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:

- SJC/TJC
- BASDAI
- BASFI
- $BASMI_{lin}$
- Maastricht AS Enthesitis Score (MASES)
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity NRS
- Patient's Assessment of Nocturnal Back Pain NRS
- Patient's Assessment of Total Back Pain NRS
- SF-36v2 Health Survey
- EQ-5D
- WPAI-axial SpA
- Patient's Global Assessment of Disease Activity NRS
- Patient's Global Assessment of Pain NRS
- Health Assessment Questionnaire modified for the Spondyloarthropathies (HAQ-S)

- Subject Dosing Diary Sheet

The adverse event eCRF data segments of: alternate etiology, severity, frequency and relationship to study drug, may also be used as source and will require an Investigator approval on the eCRF as verification of the accuracy of the information.

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 called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

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.

Medidata 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 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

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision-making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different than the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

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. Our 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. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local 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 Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last study 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:	A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis
Protocol Date:	15 January 2015

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

1. Khan MA. Update on spondyloarthropathies. Ann Intern Med. 2002;136:896-907.
2. Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? Arthritis Rheum. 2005;52(4):1000-8.
3. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-8.
4. Rudwaleit M, Haibel H, Baralaikos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009;60(3):717-27.
5. Rudwaleit M, van der Heijde D, Landewé 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.
6. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25-31.
7. Rudwaleit M, Landewé R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009;68:770-6.
8. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. Results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54(7):2136-46.

9. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondyloarthritis 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.
10. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis. 2011;70:905-8.
11. Braun J, Davis J, Dougados M, et al. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis. 2006;65:316-20.
12. Braun J, Zochling J, Baraliakos X, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. Ann Rheum Dis. 2006;65:1147 53.
13. Chen J, Liu C. Methotrexate for ankylosing spondylitis. Cochrane Database of Systematic Reviews. 2003; issue 3. Art No: CD004524.
14. Amtenbrink AL, Haibel H, Rudwaleit M, et al. Efficacy of adalimumab in the treatment of patients with axial spondyloarthritis (SPA) and no radiographic sacroiliitis: continuous adalimumab (Humira®) therapy is necessary to prevent relapses after treatment withdrawal. Ann Rheum Dis. 2008;67(Suppl II):373.
15. Song I, Hermann K, Haibel H, et al. Frequency and duration of drug-free remission after one year of Treatment with etanercept vs. sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial [abstract]. Arthritis Rheum. 2011;63 Suppl 10:S992.

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
[redacted]		Clinical
		Clinical
		Statistics
		Clinical
		Pharmacokinetics

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

In subjects with ≥ 3 months back pain^ and age at onset < 45 years

Sacroiliitis on imaging* plus ≥ 1 SpA feature#	or	HLA-B27 plus ≥ 2 SpA feature#

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

* 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†

^ Almost daily back pain.

† Subjects who fulfill the modified NY criteria for AS are excluded from the study.

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 non-steroidal anti-inflammatory drug (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

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. Epub: 2012 Jan 30.

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

Parameters used for the ASDAS:

1. Patient's assessment of total back pain (BASDAI question 2)
2. Patient global assessment of disease activity
3. Peripheral pain/swelling (BASDAI question 3)
4. Duration of morning stiffness (BASDAI question 6)
5. C-reactive protein (CRP) in mg/litre.

Calculation of ASDAS *(for reference only as IVRS/IWRS will be programmed to calculate the ASDAS)*

$ASDAS_{CRP}$: 0.121 × total back pain + 0.110 × patient global + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(CRP+1).

References:

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), 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

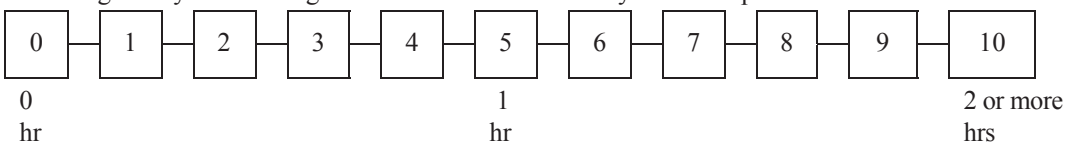
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

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?



Scoring of the BASDAI:

$$\text{BASDAI Score} = 0.2\left(\text{Item 1} + \text{Item 2} + \text{Item 3} + \text{Item 4} + \frac{\text{Item 5}}{2} + \frac{\text{Item 6}}{2}\right)$$

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.

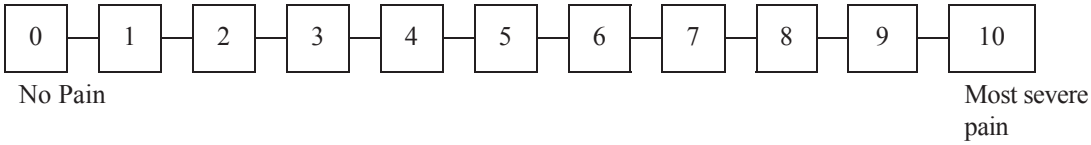
Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68;ii1-ii44. doi:10.1136/ard.2008.104018.

Appendix G. Patient's Assessment of Total Back Pain, 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?



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. doi:10.1136/ard.2008.104018.

Appendix H. Modified New York Criteria for Ankylosing Spondylitis

A. Diagnosis

1. Clinical Criteria

    a. Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.

    b. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.

    c. Limitation of chest expansion relative to normal values corrected for age and sex.

2. Radiologic Criterion

    a. Sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3-4 unilaterally.

B. Grading

1. Definite ankylosing spondylitis if the radiologic criterion is associated with at least one clinical criterion.

2. Probable ankylosing spondylitis if:

    a. Three clinical criteria are present.

    b. The radiologic criterion is present without any signs or symptoms satisfying the clinical criterion. (Other causes of sacroiliitis should be considered.)

Reference:
Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.

Appendix I. Tender and Swollen Joint Counts

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	
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 J. Linear Bath Ankylosing Spondylitis Metrology Index ($BASMI_{lin}$)

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, rolation, 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)_____

5. 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

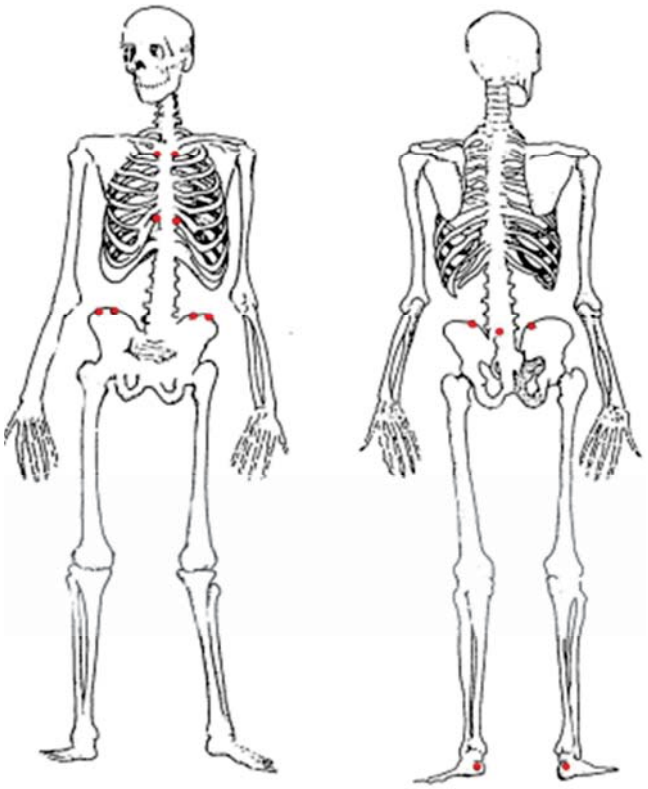
documented for future reassessments). Gravity goniometer placed centrally on the forehead. Patient rotates head as far as possible, keeping shoulders still, ensure no neck flexion or side flexion occurs. Rotational angled to the right and to the left is measured.

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;489-493. Epub 2007 Aug 29.

Appendix K. Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)



1st Costochondral joint left/right
7th Costochondral joint left/right
Posterior superior iliac spine left/right
Anterior superior iliac spine left/right
Iliac crest left/right
5th 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 L. Bath Ankylosing Spondylitis Functional Index (BASFI), 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

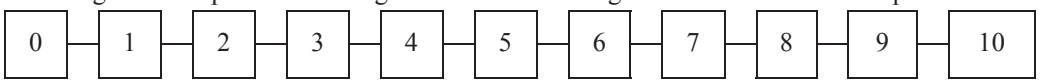
5. Getting up off the floor without help from lying on your back.

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

6. Standing unsupported for 10 minutes without discomfort.

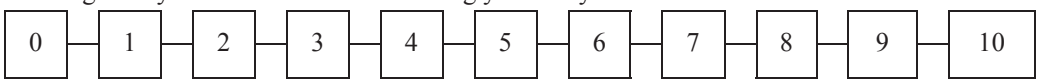
0	1	2	3	4	5	6	7	8	9	10
easy										impossible

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



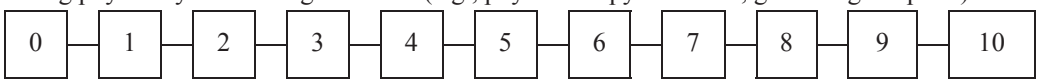
easy impossible

8. Looking over your shoulder without turning your body.



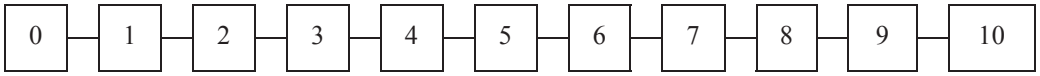
easy impossible

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



easy impossible

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



easy impossible

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. doi:10.1136/ard.2008.104018.

Appendix M. Physician's Global Assessment of Disease Activity, NRS

Please mark a 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. doi:10.1136/ard.2008.104018.

Appendix N. Patient's Assessment of Nocturnal Back Pain, 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. doi:10.1136/ard.2008.104018.

Appendix O. Patient's Global Assessment of Disease Activity, NRS

Please place a mark in the box below to indicate your answer (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										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. doi:10.1136/ard.2008.104018.

Appendix P. Patient's Global Assessment of Pain, 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 Q. Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

Modified Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S)

Place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING AND GROOMING **Are you able to:**				
Dress yourself, including shoelaces and buttons?	☐ 0	☐ 1	☐ 2	☐ 3
Shampoo your hair?	☐ 0	☐ 1	☐ 2	☐ 3
ARISING **Are you able to:**				
Stand up from a straight chair?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of bed?	☐ 0	☐ 1	☐ 2	☐ 3
EATING **Are you able to:**				
Cut your own meat?	☐ 0	☐ 1	☐ 2	☐ 3
Lift a full cup or glass to your mouth?	☐ 0	☐ 1	☐ 2	☐ 3
Open a new milk carton?	☐ 0	☐ 1	☐ 2	☐ 3
WALKING **Are you able to:**				
Walk outdoors on a flat ground?	☐ 0	☐ 1	☐ 2	☐ 3
Climb up five steps?	☐ 0	☐ 1	☐ 2	☐ 3

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for dressing (button hook, zipper pull etc.)	☐ Built up or special utensils	☐ Crutches
☐ Special or built up chair	☐ Cane	☐ Wheelchair
☐ Walker		

Place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE **Are you able to:**				
Wash and dry your body?	☐ 0	☐ 1	☐ 2	☐ 3
Take a tub bath?	☐ 0	☐ 1	☐ 2	☐ 3
Get on and off the toilet?	☐ 0	☐ 1	☐ 2	☐ 3
REACH **Are you able to:**				
Reach and get down a 5 pound (2.3 kilo) object (such as a bag of sugar) from above your head?	☐ 0	☐ 1	☐ 2	☐ 3
Bend down to pick up clothing from the floor?	☐ 0	☐ 1	☐ 2	☐ 3
GRIP **Are you able to:**				
Open car doors?	☐ 0	☐ 1	☐ 2	☐ 3
Open previously opened jars?	☐ 0	☐ 1	☐ 2	☐ 3
Turn faucets on and off?	☐ 0	☐ 1	☐ 2	☐ 3
ACTIVITIES **Are you able to:**				
Run errands and shop?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of a car?	☐ 0	☐ 1	☐ 2	☐ 3
Do chores such as vacuuming or yard work?	☐ 0	☐ 1	☐ 2	☐ 3
Are you able to carry heavy packages such as grocery bags?	☐ 0	☐ 1	☐ 2	☐ 3
Are you able to sit for long periods of time, such as at work?	☐ 0	☐ 1	☐ 2	☐ 3
Are you able to work at a flat topped Table or desk?	☐ 0	☐ 1	☐ 2	☐ 3
DRIVING A CAR **Check here _____ if you DO NOT have a driver's license or a car**				
Are you able to look in the rear view mirror?	☐ 0	☐ 1	☐ 2	☐ 3
Are you able to turn your head to drive in reverse?	☐ 0	☐ 1	☐ 2	☐ 3

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat	☐ Bathtub bar	☐ Long-handled appliances for reach
☐ Bathtub seat	☐ Long-handled appliances in bathroom	☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

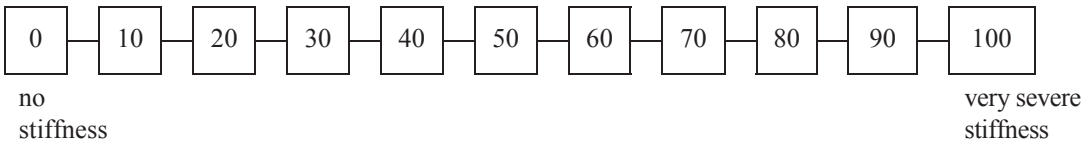
Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain,") please record the number below.

☐☐☐

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

☐☐☐

How much **stiffness** have you had because of your illness in the past week? Place a mark to indicate the severity of the stiffness. (i.e., 10)



Reference:

Daltroy LH, Larson MG, Roberts NW, et al. A modification of the Health Assessment Questionnaire for the spondyloarthropathies. J Rheumatol. 1990;17(7):946-50.

Appendix R. SF-36v2 Health Status Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to 1 year ago, how would you rate your health in general now?

Much better now than 1 year ago	Somewhat better now than 1 year ago	About the same as 1 year ago	Somewhat worse now than 1 year ago	Much worse now than 1 year ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

SF-36v2™ Standards, US Version 2.0

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36v2™ Standards, US Version 2.0

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36v2™ Standards, US Version 2.0

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

SF-36v2™ Standards, US Version 2.0

Appendix S. Work Productivity and Activity Impairment Questionnaire: Axial Spondylorarthritis, V2.0 (WPAI: Axial Spondyloarthritis)

Page 1 of 2

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.

Work Productivity and Activity Impairment Questionnaire: Axial Spondylorarthritis, V2.0 (WPAI: Axial Spondyloarthritis)

(Page 2 of 2)

Consider only how much <u>axial spondyloarthritis</u> affected productivity <u>while you were working</u>.

Axial Spondyloarthritis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Axial Spondyloarthritis completely prevented me from 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 <u>axial spondyloarthritis</u> affected your ability to do your regular daily activities, other than work at a job.

Axial Spondyloarthritis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Axial Spondyloarthritis completely prevented me from doing my daily activities

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 T. EQ-5D (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 ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

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

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

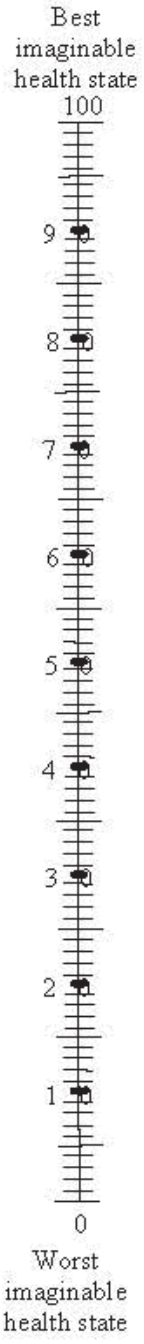
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

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. 2nd ed. 1996;9:480-483.

Appendix U. 70-Day Follow-Up Call – Sample

Site Name/Number: _____
Subject Number: _____

Please contact subjects that discontinue adalimumab 70 days following 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 V. Injection Instructions – Sample Pre-Filled Syringe

Subject Instructions

0.8 mL dose

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

Protocol M13-375

Tables of Contents

Study Drug Dosing Schedule

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study. You will receive a kit each visit containing 2 syringes.

You will receive the following number of injections during this study:

- Baseline visit (the first visit to receive study medication for this study) you will receive 1 injection at the clinic (self administer or receive help from site staff).
- Weeks 2, 4, 8, 12 and 24 you will administer 1 injection at the clinic to allow site staff to view your injection technique. It is possible that you may be discontinued at Weeks 20, 24 or 28 if you do not qualify to continue by meeting the remission criteria.
- Weeks 6, 10, 14, 16, 18, 20, 22 and 26 you will administer 1 injection at home or clinic if applicable. *Note on clinic days, you must inject study drug after all study procedures are performed (not prior)*.
- If Randomized at Week 28, you will administer 1 injection every other week (eow) at home (or in clinic), Week 28 through the end of the study (Week 68-80 based on Rescue Therapy needed).

During the Baseline Visit through Week 26, you will receive active study medication. You or a trained designee will inject your study drug every other week from the Baseline Visit to Week 26.

During the Week 28 Visit, if you have meet criteria for Randomization, you will receive 1 kit (2 syringes) of blinded study medication each visit from Week 28 through Week 66 to be injected at home. You will not administer study medication at your last visit (Week 68).

If you meet the criteria for flare on 2 consecutive visits, you will receive rescue therapy (active study drug) until the end of the study. If you flare at Weeks 60, 64 or 68, you will

receive rescue therapy for 12 weeks and will receive rescue therapy until Weeks 72, 76 or 80 respectively. 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" during the open-label period (Period 1) or during rescue therapy and "Adalimumab or Placebo" during the double-blind period (Period 2).
- Store all pre-filled syringes in your refrigerator at 36°F to 46°F (2°C 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

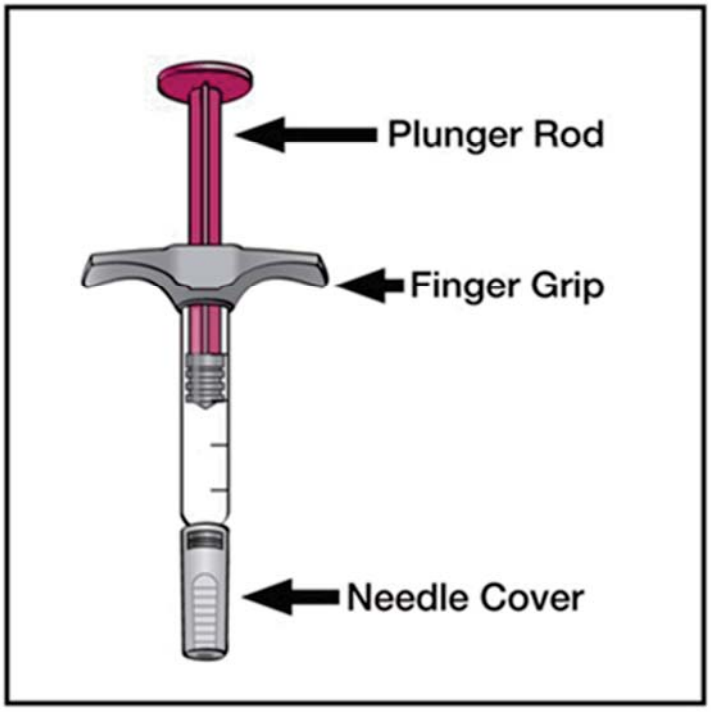
- Find a clean flat surface.
- Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one kit with the prefilled syringe(s) of study drug from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been 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:

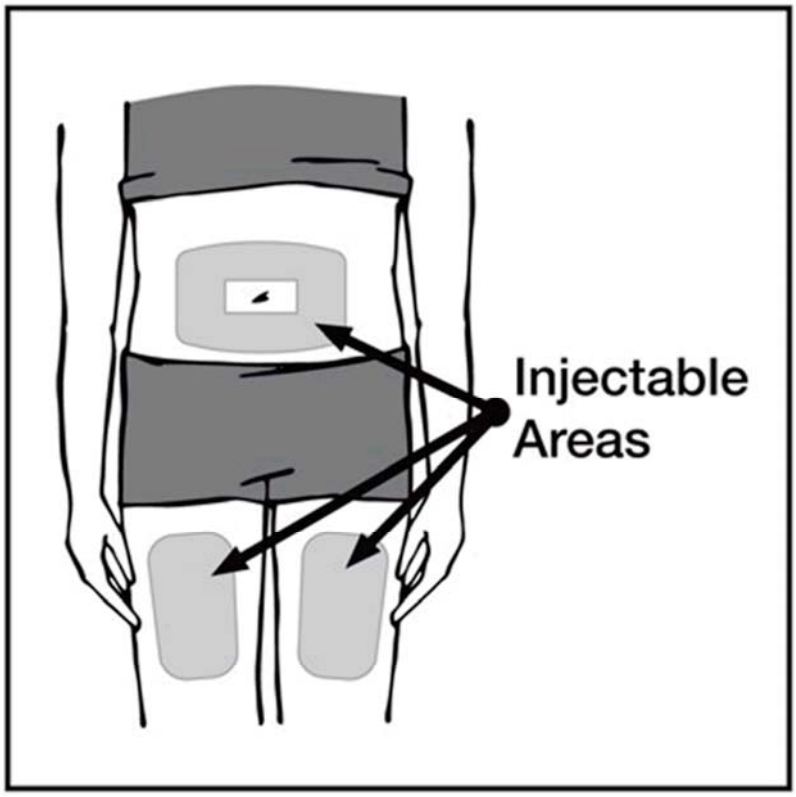
- the seals on top and bottom of the carton are broken or missing.
- the study medication labeling has an expired date. Check the expiration date on your study medication carton and do not use if the date has passed.
- the prefilled syringe has been frozen or left in direct sunlight.
- the liquid in 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.

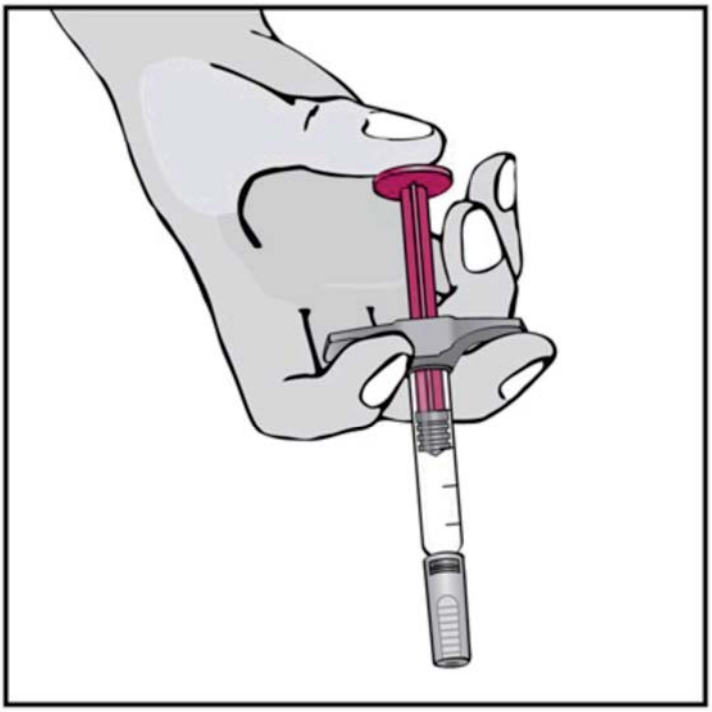


- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject into skin that is:
  - sore (tender)
  - bruised
  - red
  - hard
  - scarred or where you have stretch marks
- If you have psoriasis, 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

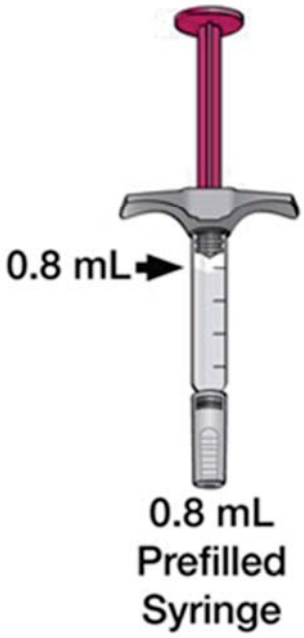
- Check the fluid level in the syringe:
  - Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

Figure C.



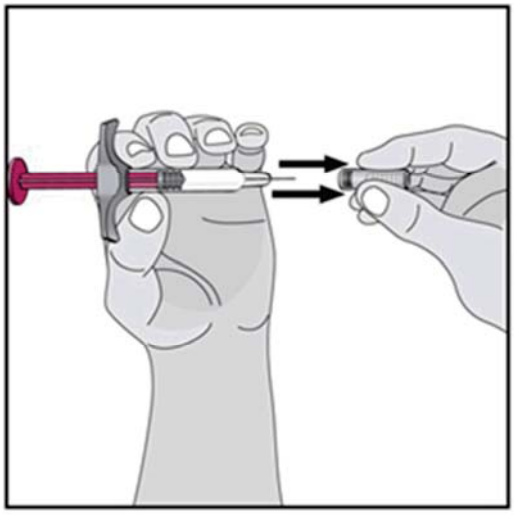
Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg prefilled syringe. See Figure D.

Figure D.



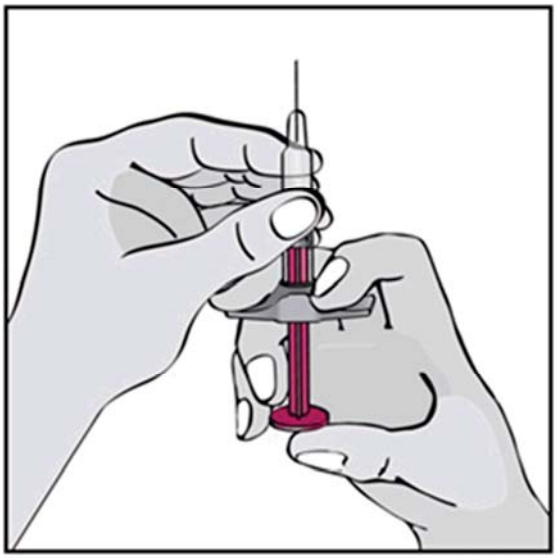
- The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.
- Remove the needle cover:
  - Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure E.
  - Throw away the needle cover.

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.

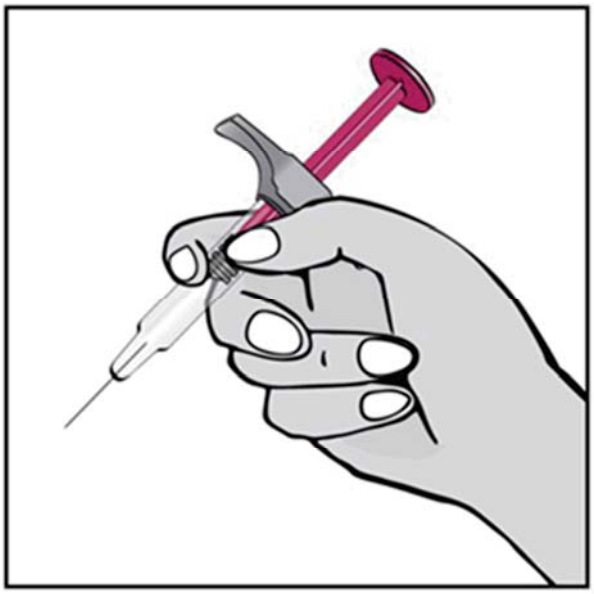


- You may see a drop of liquid at the end of the needle. This is normal.
- Do not shake the syringe.

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.

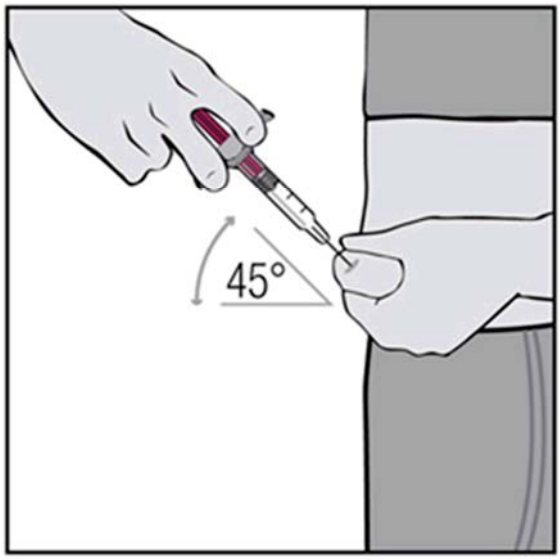


- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly. See Figure H.

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.

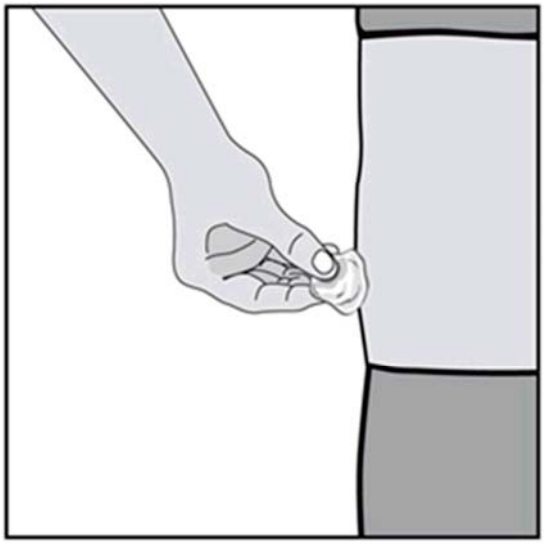


- After the needle is in, let go of the skin. Pull back gently on the plunger.

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.

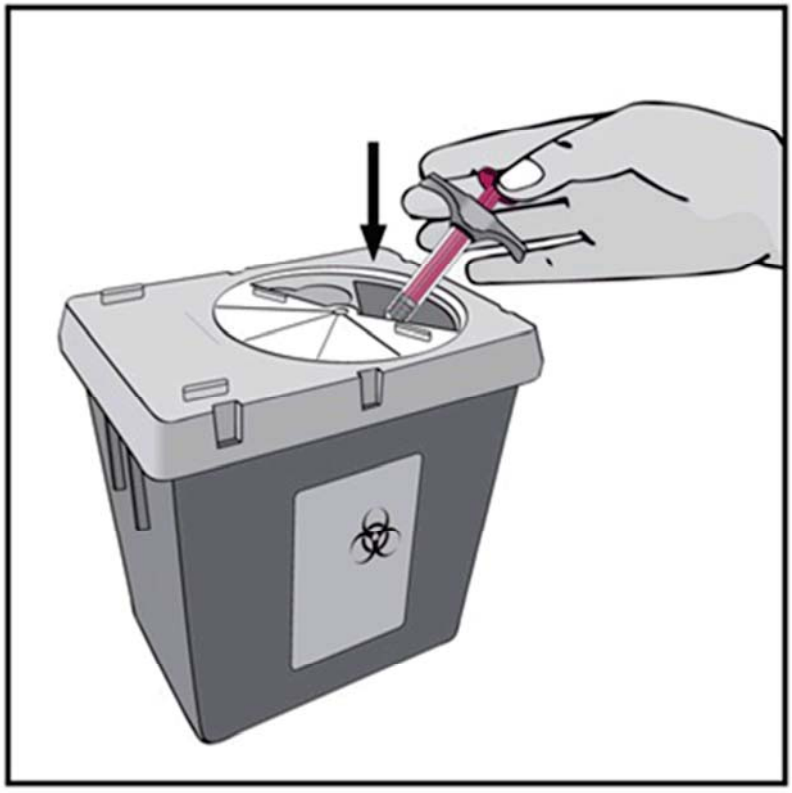


- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 12 with a new prefilled syringe.

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 W. 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[a]	Kit Number	Dose (mL) Administered	Injection Site (abdomen or thigh)	Initials of Person Administering Study Medication	Comments
31/MAY/12	*EXAMPLE*	*0 9:3 0 hrs*	*123456*	*0.8 mL*	*abdomen*	*PG*	*Clinic injection*
	Baseline	_ _ : _ _ hrs					
	Week 2	_ _ : _ _ hrs					
	Week 4	_ _ : _ _ hrs					
	Week 6	_ _ : _ _ hrs					
	Week 8	_ _ : _ _ hrs					
	Week 10	_ _ : _ _ hrs					
	Week 12	_ _ : _ _ hrs					
	Week 14	_ _ : _ _ hrs					
	Week 16	_ _ : _ _ hrs					
	Week 18	_ _ : _ _ hrs					
	Week 20	_ _ : _ _ hrs					
	Week 22	_ _ : _ _ hrs					
	Week 24	_ _ : _ _ hrs					
	Week 26	_ _ : _ _ hrs					
	Week 28	_ _ : _ _ hrs					
	Week 30	_ _ : _ _ hrs					
	Week 32	_ _ : _ _ hrs					
	Week 34	_ _ : _ _ hrs					
	Week 36	_ _ : _ _ hrs					
	Week 38	_ _ : _ _ hrs					
	Week 40	_ _ : _ _ hrs					
	Week 42	_ _ : _ _ hrs					
	Week 44	_ _ : _ _ hrs					
	Week 46	_ _ : _ _ hrs					
	Week 48	_ _ : _ _ hrs					
	Week 50	_ _ : _ _ hrs					
	Week 52	_ _ : _ _ hrs					
	Week 54	_ _ : _ _ hrs					
	Week 56	_ _ : _ _ hrs					
	Week 58	_ _ : _ _ hrs					

Date day/mm/yr	Day or Week[#]	Time of Study Drug Administration[a]	Kit Number	Dose (mL) Administered	Injection Site (abdomen or thigh)	Initials of Person Administering Study Medication	Comments
	Week 60	_ _ : _ _ hrs					
	Week 62	_ _ : _ _ hrs					
	Week 64	_ _ : _ _ hrs					
	Week 66	_ _ : _ _ hrs					
	Week 68	_ _ : _ _ hrs					
	Week 70	_ _ : _ _ hrs					
	Week 72	_ _ : _ _ hrs					
	Week 74	_ _ : _ _ hrs					
	Week 76	_ _ : _ _ hrs					
	Week 78	_ _ : _ _ hrs					

a. Please note the time in military time (e.g., 22:00 hrs etc.)

Appendix X. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	[redacted]

Has been changed to read:

Sponsor/Emergency Contact:	[redacted]

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M13-375
Name of Study Drug: Adalimumab	**Phase of Development:** 3b/4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 04 December 2013
Protocol Title: A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis	
Objective: The objective of this study is to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given every other week (eow) subcutaneously (SC) in maintaining remission in subjects with non-radiographic axial Spondyloarthritis (nr-axSpA).	
Investigators: Multicenter	
Study Sites: Approximately 150 sites	
Study Population: Adult subjects with nr-axSpA and objective evidence of active inflammation in the sacroiliac (SI) joints or spine on MRI, or elevated high sensitivity C-reactive protein (hs-CRP).	
Number of Subjects to be Enrolled: Approximately 740	

Methodology:

The study duration will include a 30-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40-week double-blind, placebo-controlled treatment period (Period 2), with an opportunity to receive at least 12 weeks of rescue therapy (subjects who flare at Weeks 60, 64 and 68 will be allowed 12 weeks of rescue therapy), and a 70-day follow-up phone call.

Subjects in remission defined as meeting Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease (ASDAS < 1.3) at Weeks 16, 20, 24 and Week 28 will be randomized in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo during Period 2. Due to the importance of the Week 16, 20 and 24 visits, two or more missed visits during this time must be discussed with the AbbVie Medical Monitor prior to randomization. If a subject misses a single visit at Week 16, 20, or 24 the site will need to use the ASDAS parameters from the visit immediately prior to the missed visit. If a subject misses the Week 28 visit, the subject must be discontinued. Subjects not meeting the ASDAS Inactive Disease at Weeks 16, 20, 24 or Week 28 will be discontinued. Subjects may be discontinued as early as Week 20 if they do not meet the ASDAS remission criteria using the Week 16 parameters.

No formal unblinded interim analysis is planned for this study that requires an adjustment to the *P* value. An interim analysis will be performed when all ongoing subjects have completed at least Week 28 of the study. The primary and secondary endpoints of the study from the double-blind period will be reported at the completion of the study.

Subjects who flare in Period 2 (40-week double-blind period) will be allowed rescue therapy. Flare is defined as 2 consecutive study visits with ASDAS ≥ 2.1. Rescue therapy will consist of OL adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. After 12 weeks of rescue therapy with OL adalimumab eow, initiation of or change in a subject's concomitant medications for SpA including doses of DMARDs, corticosteroids, NSAIDs, and analgesics are permitted based on the investigator's medical judgment. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject age ≥ 18 years.
2. Subject with nr-axSpA fulfilling the Assessment of Spondyloarthritis International Society (ASAS) axial SpA classification criteria, but not fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis.
3. Subject has had an inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs) over a 4-week period in total at maximum recommended or tolerated doses, or has intolerance to or a contraindication for NSAIDs as defined by the Investigator.
4. Subject with objective evidence of active inflammation in the SI joints or spine on MRI or elevated hs-CRP at screening (elevated hs-CRP is defined as any level greater than the upper limit of normal for the lab).
5. Subject is a candidate for anti-TNF therapy based on the investigator's opinion.
6. Subjects must have baseline disease activity as defined by having an ASDAS ≥ 2.1 (note, sites will need to use the Screening Visit hs-CRP to calculate ASDAS at Screening and Baseline Visits with the remainder of parameters visit-specific), BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits.

Main Exclusion:

1. Subject fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis at or prior to the Screening Visit.
2. 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.
3. If entering the study on concomitant disease-modifying anti-rheumatic drugs (DMARDs), subject not on stable dose of methotrexate (≤ 25 mg per week) and/or sulfasalazine (≤ 3 g per day) and/or hydroxychloroquine (≤ 400 mg per day) for 28 days prior to the Baseline Visit. All other oral DMARDs are prohibited within 28 days prior to the Baseline Visit.
4. If entering the study on concomitant azathioprine (AZA), subject not on stable dose (≤ 150 mg per day) for 28 days prior to the Baseline Visit or is on AZA and another concomitant immunosuppressive drug at study entry.
5. If entering the study on concomitant NSAIDs, tramadol, and/or non-opioid analgesics, subject not on stable doses for 14 days prior to the Baseline Visit.
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 not on stable dose of prednisone (≤ 10 mg per day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
8. Subject has been treated with intramuscular, 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.

Main Exclusion (Continued): 10. Subject with extra-articular manifestations (e.g., inflammatory bowel disease, psoriasis, uveitis, etc.) that is not clinically stable for at least 30 days prior to study entry. 11. Subject has a history of fibromyalgia or inflammatory arthritis of a different etiology other than SpA (e.g., rheumatoid arthritis, gout, systemic lupus erythematosus, polyarticular or systemic juvenile idiopathic arthritis).	
Investigational Product:	Adalimumab
Dose:	40 mg eow
Mode of Administration:	SC
Reference Therapy:	Placebo
Dose:	eow
Mode of Administration:	SC
Duration of Treatment: Length of exposure will depend on remission or flare status (20 [first time ASDAS remission will be calculated] to 80 weeks of treatment). The duration of treatment will include a 28-week, OL period (adalimumab 40 mg eow), followed by a 40-week, randomized, double-blind period (adalimumab 40 mg eow versus placebo), with an opportunity to receive at least 12 weeks of rescue therapy (subjects who flare at Weeks 60, 64 or 68 will be allowed 12 weeks of rescue therapy and final study visit will be at Weeks 72, 76, or 80, respectively).	
Criteria for Evaluation: **Efficacy:** The primary efficacy variable is the proportion of subjects who do not experience a flare by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS ≥ 2.1. Secondary efficacy variables include the following: At 12 weeks after initiation of Rescue Therapy • ASDAS Inactive Disease (ASDAS < 1.3) • ASDAS Major Improvement (a change from baseline ≤ –2.00) • ASDAS Clinically Important Improvement (a change from baseline ≤ –1.10)	

Efficacy (Continued):

- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
  - ASAS20 response: improvement of ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit)
    - Patient's Global Assessment – Represented by the PTGA-disease activity NRS score (0 to 10)
    - Pain – Represented by the patient's assessment of total back pain NRS score (0 to 10)
    - Function – Represented by the BASFI NRS score (0 to 10)
    - Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10])
  - ASAS40 response: improvement of ≥ 40% and absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in ≥ 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain
  - ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20
  - ASAS 5/6 response: 20% improvement from Baseline in 5 out of the following 6 domains: BASFI, patient's assessment of total back pain, PTGA-disease activity, inflammation (mean of items 5 and 6 of the BASDAI), lateral lumbar flexion from BASMI, and hs-CRP
- Bath AS Disease Activity Index 50 (BASDAI50)
- Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

At Week 28 and Week 68

- ASDAS Inactive Disease
- ASDAS Major Improvement
- ASDAS Clinically Important Improvement
- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
- BASDAI50
- HAQ-S

At Week 68

- Time to flare defined as ASDAS ≥ 2.1 at 2 consecutive visits
- Time to partial flare defined as ASDAS ≥ 1.3 but < 2.1 at 2 consecutive visits
- Proportion of subjects who reach flare definition
- Proportion of subjects who reach partial flare definition

<u>Other Efficacy Variables</u>

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of Total back pain
- Bath AS Functional Index (BASFI)
- Inflammation/Morning Stiffness (mean of BASDAI questions 5 and 6)

Efficacy (Continued):

- Bath AS Disease Activity Index (BASDAI)
- ASDAS
- hs-CRP
- Linear Bath AS Metrology Index ($BASMI_{lin}$)
- Swollen Joint Count (66 joints)
- Tender Joint Count (68 joints)
- MASES
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Pain
- Patient's Assessment of Nocturnal Back Pain
- Anterior Uveitis
- Short Form-36v2 Health Survey questionnaire
- EQ-5D
- Work Productivity and Activity Impairment – Axial Spondylorarthritis (WPAI-axial SpA)
- SPARCC scores for MRI of the SI joint and spine
- Proportion of subjects who regain remission on rescue therapy
- Time to regain remission on rescue therapy

Each subject will have blood drawn for biomarkers at the following time points: Baseline, Week 28, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit. The biomarkers may include the following:

- DKK-1
- Sclerostin
- BMP-2
- BMP-7

Pharmacokinetic:

Each subject will have blood drawn for serum adalimumab concentration and anti-adalimumab antibody (AAA) at the following time points: Baseline, Weeks 12, 28, 36, 52, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit.

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, vital signs, physical examination (if required) and laboratory tests.

Statistical Methods:

Efficacy:

The primary efficacy variable is the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study between the adalimumab and placebo groups. Analysis will be performed using a two-sided chi squared test with an $\alpha = 0.05$. Subjects with missing primary efficacy endpoint response at Week 68 will be treated as non-responders, i.e., a "non-responder imputation" criterion will be used for missing data. Descriptive statistics will also be provided for primary and secondary efficacy variables.

Pharmacokinetic:

For each scheduled time of measurement, summary statistics will be provided for the adalimumab serum concentration data by treatment group. The adalimumab concentration data may be analyzed using nonlinear mixed effects modeling approach. The percentage of subjects with AAA will be reported.

Safety:

Safety analyses will be carried out using the safety population, which includes all subjects who received at least one dose of study medication. 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 first dose of the study medication, and up to within 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 body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. In addition, summary of AEs by severity and relationship to study drug will be presented. Serious, severe, or AEs that lead to premature study discontinuation will be listed.

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 prior to the first dose of study drug 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:

Assuming that 50% of subjects treated with adalimumab will not experience any flare up to Week 68, 120 subjects per arm are required for the double-blind period (Period 2) (with an adjustment for a drop-out rate of no more than 30%) is targeted to result in at least 90% power for detecting 25% difference at Week 68 primary endpoint between adalimumab and placebo based on a two-sided test with significance level 0.05.

It is assumed that approximately 33% of the subjects enrolled into the OL period (Period 1) would meet ASDAS Inactive Disease at Weeks 16, 20, 24 and Week 28; therefore, a total of approximately 740 subjects would be required to be enrolled in order to have sufficient number of subjects (i.e., 120 subjects per arm) for the double-blind period. Study enrollment will be closed prior to reaching 740 subjects should a sufficient number of subjects fulfill remission criteria and be available for randomization at the end of Period 1 prior to full enrollment.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M13-375
Name of Study Drug: Adalimumab	**Phase of Development:** 3b/4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 15 January 2015
Protocol Title: A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis	
Objective: The objective of this study is to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given every other week (eow) subcutaneously (SC) in maintaining remission in subjects with non-radiographic axial Spondyloarthritis (nr-axSpA).	
Investigators: Multicenter	
Study Sites: Approximately 150 sites	
Study Population: Adult subjects with nr-axSpA and objective evidence of active inflammation in the sacroiliac (SI) joints or spine on MRI, or elevated high sensitivity C-reactive protein (hs-CRP).	
Number of Subjects to be Enrolled: Approximately 740	
Methodology: The study duration will include a 42-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40-week double-blind, placebo-controlled treatment period (Period 2), with an opportunity to receive at least 12 weeks of rescue therapy (subjects who flare at Weeks 60, 64 and 68 will be allowed 12 weeks of rescue therapy), and a 70-day follow-up phone call. Subjects in remission defined as meeting Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease (ASDAS < 1.300) at Weeks 16, 20, 24 and Week 28 will be randomized in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo during Period 2. Due to the importance of the Week 16, 20 and 24 visits, two or more missed visits during this time must be discussed with the AbbVie Medical Monitor prior to randomization. If a subject misses a single visit at Week 16, 20, or 24 the site will need to use the ASDAS parameters from the visit immediately prior to the missed visit. If a subject misses the Week 28 visit, the subject must be discontinued. Subjects not meeting the ASDAS Inactive Disease at Weeks 16, 20, 24 or Week 28 will be discontinued. Subjects may be discontinued as early as Week 20 if they do not meet the ASDAS remission criteria using the Week 16 parameters. No formal unblinded interim analysis is planned for this study that requires an adjustment to the *P* value. An interim analysis will be performed when all ongoing subjects have completed at least Week 28 of the study. The primary and secondary endpoints of the study from the double-blind period will be reported at the completion of the study. Subjects who flare in Period 2 (40-week double-blind period) will be allowed rescue therapy. Flare is defined as 2 consecutive study visits with ASDAS ≥ 2.100. Rescue therapy will consist of OL adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study. After 12 weeks of rescue therapy with OL adalimumab eow, initiation of or change in a subject's concomitant medications for SpA including doses of DMARDs, corticosteroids, NSAIDs, and analgesics are permitted based on the investigator's medical judgment. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject age ≥ 18 years.
2. Subject with nr-axSpA fulfilling the Assessment of Spondyloarthritis International Society (ASAS) axial SpA classification criteria, but not fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis.
3. Subject has had an inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs) over a 4-week period in total at maximum recommended or tolerated doses, or has intolerance to or a contraindication for NSAIDs as defined by the Investigator.
4. Subject with objective evidence of active inflammation in the SI joints or spine on MRI or elevated hs-CRP at screening (elevated hs-CRP is defined as any level greater than the upper limit of normal for the lab).
5. Subject is a candidate for anti-TNF therapy based on the investigator's opinion.
6. Subjects must have baseline disease activity as defined by having an ASDAS ≥ 2.100 (note, sites will need to use the Screening Visit hs-CRP to calculate ASDAS at Screening and Baseline Visits with the remainder of parameters visit-specific), BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits.

Main Exclusion:

1. Subject fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis at or prior to the Screening Visit.
2. 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.
3. If entering the study on concomitant disease-modifying anti-rheumatic drugs (DMARDs), subject not on stable dose of methotrexate (≤ 25 mg per week) and/or sulfasalazine (≤ 3 g per day) and/or hydroxychloroquine (≤ 400 mg per day) for 28 days prior to the Baseline Visit. All other oral DMARDs, with the exception of azathioprine or mercaptopurine (6-MP) are prohibited within 28 days prior to the Baseline Visit.
4. If entering the study on concomitant azathioprine (AZA) or 6-MP, subject not on stable dose (AZA ≤ 150 mg per day or 6-MP ≤ 75 mg per day) for 28 days prior to the Baseline Visit or is on AZA or 6-MP and another concomitant immunosuppressive drug at study entry.
5. If entering the study on concomitant NSAIDs, tramadol, and/or non-opioid analgesics, subject not on stable doses for 14 days prior to the Baseline Visit.
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 not on stable dose of prednisone (≤ 10 mg per day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
8. Subject has been treated with intramuscular, intra-articular joint injection(s) or spinal/paraspinal injection(s) of corticosteroids in the preceding 28 days prior to the Baseline Visit.

Main Exclusion (Continued): 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 with extra-articular manifestations (e.g., inflammatory bowel disease, psoriasis, uveitis, etc.) that is not clinically stable for at least 30 days prior to study entry. 11. Subject has a history of fibromyalgia or inflammatory arthritis of a different etiology other than SpA (e.g., rheumatoid arthritis, gout, systemic lupus erythematosus, polyarticular or systemic juvenile idiopathic arthritis).	
Investigational Product:	Adalimumab
Dose:	40 mg eow
Mode of Administration:	SC
Reference Therapy:	Placebo
Dose:	eow
Mode of Administration:	SC
Duration of Treatment: Length of exposure will depend on remission or flare status (20 [first time ASDAS remission will be calculated] to 80 weeks of treatment). The duration of treatment will include a 28-week, OL period (adalimumab 40 mg eow), followed by a 40-week, randomized, double-blind period (adalimumab 40 mg eow versus placebo), with an opportunity to receive at least 12 weeks of rescue therapy (subjects who flare at Weeks 60, 64 or 68 will be allowed 12 weeks of rescue therapy and final study visit will be at Weeks 72, 76, or 80, respectively).	
Criteria for Evaluation: **Efficacy:** The primary efficacy variable is the proportion of subjects who do not experience a flare by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS $\geq$ 2.100. Secondary efficacy variables include the following: At 12 weeks after initiation of Rescue Therapy • ASDAS Inactive Disease (ASDAS < 1.300) • ASDAS Major Improvement (a change from baseline $\leq$ –2.000) • ASDAS Clinically Important Improvement (a change from baseline $\leq$ –1.100)	

Efficacy (Continued):

- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
  - ASAS20 response: improvement of ≥ 20% and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in ≥ 3 of the following 4 domains, with no deterioration in the remaining domain (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit)
    - Patient's Global Assessment – Represented by the PTGA-disease activity NRS score (0 to 10)
    - Pain – Represented by the patient's assessment of total back pain NRS score (0 to 10)
    - Function – Represented by the BASFI NRS score (0 to 10)
    - Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10])
  - ASAS40 response: improvement of ≥ 40% and absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in ≥ 3 of the 4 domains above in ASAS20 with no deterioration in the potential remaining domain
  - ASAS partial remission: absolute score of < 2 units for each of the 4 domains identified above in ASAS20
  - ASAS 5/6 response: 20% improvement from Baseline in 5 out of the following 6 domains: BASFI, patient's assessment of total back pain, PTGA-disease activity, inflammation (mean of items 5 and 6 of the BASDAI), lateral lumbar flexion from BASMI, and hs-CRP
- Bath AS Disease Activity Index 50 (BASDAI50)
- Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

At Week 28 and Week 68

- ASDAS Inactive Disease
- ASDAS Major Improvement
- ASDAS Clinically Important Improvement
- ASAS20, ASAS40, ASAS 5/6 and ASAS Partial Remission
- BASDAI50
- HAQ-S

At Week 68

- Time to flare defined as ASDAS ≥ 2.100 at 2 consecutive visits
- Time to partial flare defined as ASDAS ≥ 1.300 but < 2.100 at 2 consecutive visits
- Proportion of subjects who reach flare definition
- Proportion of subjects who reach partial flare definition

<u>Other Efficacy Variables</u>

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of Total back pain
- Bath AS Functional Index (BASFI)
- Inflammation/Morning Stiffness (mean of BASDAI questions 5 and 6)

Efficacy (Continued):

- Bath AS Disease Activity Index (BASDAI)
- ASDAS
- hs-CRP
- Linear Bath AS Metrology Index ($BASMI_{lin}$)
- Swollen Joint Count (66 joints)
- Tender Joint Count (68 joints)
- MASES
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Pain
- Patient's Assessment of Nocturnal Back Pain
- Anterior Uveitis
- Short Form-36v2 Health Survey questionnaire
- EQ-5D
- Work Productivity and Activity Impairment – Axial Spondylorarthritis (WPAI-axial SpA)
- SPARCC scores for MRI of the SI joint and spine
- Proportion of subjects who regain remission on rescue therapy
- Time to regain remission on rescue therapy

Exploratory Variables:

Each subject will have blood drawn for biomarkers at the following time points: Baseline, Weeks 28, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit. The final set of biomarkers to be analyzed may include the following:

- DKK-1
- Sclerostin
- BMP-2
- BMP-7

The final selection of biomarkers for analysis will be based on both insights gained in the sub-study and available scientific knowledge at study completion.

Pharmacokinetic:

Each subject will have blood drawn for serum adalimumab concentration and anti-adalimumab antibody (AAA) at the following time points: Baseline, Weeks 12, 28, 36, 52, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit.

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, vital signs, physical examination (if required) and laboratory tests.

Statistical Methods:

Efficacy:

The primary efficacy variable is the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study between the adalimumab and placebo groups. Analysis will be performed using a two-sided chi squared test with an $\alpha = 0.05$. Subjects with missing primary efficacy endpoint response at Week 68 will be treated as non-responders, i.e., a "non-responder imputation" criterion will be used for missing data. Descriptive statistics will also be provided for primary and secondary efficacy variables.

Pharmacokinetic:

For each scheduled time of measurement, summary statistics will be provided for the adalimumab serum concentration data by treatment group. The adalimumab concentration data may be analyzed using nonlinear mixed effects modeling approach. The percentage of subjects with AAA will be reported.

Safety:

Safety analyses will be carried out using the safety population, which includes all subjects who received at least one dose of study medication. 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 first dose of the study medication, and up to within 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 body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. In addition, summary of AEs by severity and relationship to study drug will be presented. Serious, severe, or AEs that lead to premature study discontinuation will be listed.

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 prior to the first dose of study drug 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:

Assuming that 50% of subjects treated with adalimumab will not experience any flare up to Week 68, 120 subjects per arm are required for the double-blind period (Period 2) (with an adjustment for a drop-out rate of no more than 30%) is targeted to result in at least 90% power for detecting 25% difference at Week 68 primary endpoint between adalimumab and placebo based on a two-sided test with significance level 0.05.

It is assumed that approximately 33% of the subjects enrolled into the OL period (Period 1) would meet ASDAS Inactive Disease at Weeks 16, 20, 24 and Week 28; therefore, a total of approximately 740 subjects would be required to be enrolled in order to have sufficient number of subjects (i.e., 120 subjects per arm) for the double-blind period. Study enrollment will be closed prior to reaching 740 subjects should a sufficient number of subjects fulfill remission criteria and be available for randomization at the end of Period 1 prior to full enrollment.

Section 1.3 List of Abbreviations and Definition of Terms
Add: new abbreviation

6-MP	6-mercaptopurine

Section 3.3 Adalimumab Overview
Last paragraph, second and third sentence previously read:

Additional indications have been approved in the US and EU including Psoriasis, PsA, AS, Crohn's Disease (CD), Ulcerative Colitis (UC), and Polyarticular Juvenile Idiopathic Arthritis. In addition, an indication for nr-axSpA has been approved in the EU.

Has been changed to read:

Additional indications have been approved in the US and EU including Psoriasis, PsA, AS, Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), and Polyarticular Juvenile Idiopathic Arthritis. In addition, an indication for nr-axSpA and Pediatric Enthesitis-Related Arthritis has been approved in the EU.

Section 3.6 Benefits and Risks
Fifth sentence previously read:

For Study M13-375, to ensure nr-axSpA subjects are appropriate candidates for anti-TNF therapy subjects are required to meet a minimum level of disease activity at baseline (ASDAS ≥ 2.1, BASDAI ≥ 4, Patient's Assessment of Total Back Pain score ≥ 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), and have had an inadequate response to at least 2 NSAIDs.

Has been changed to read:

For Study M13-375, to ensure nr-axSpA subjects are appropriate candidates for anti-TNF therapy subjects are required to meet a minimum level of disease activity at baseline (ASDAS ≥ 2.100, BASDAI ≥ 4, Patient's Assessment of Total Back Pain score ≥ 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), and have had an inadequate response to at least 2 NSAIDs.

Section 5.1 Overall Study Design and Plan: Description
First paragraph, first sentence previously read:

The study duration will include a 30-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40 week double-blind placebo controlled eow treatment period (Period 2) with an opportunity to receive at least 12 weeks of rescue therapy (subjects that flare at Weeks 60, 64 or 68 will be allowed 12 weeks of rescue therapy and final visits will be 72, 76 or 80 respectively), plus a 70-day follow-up phone call.

Has been changed to read:

The study duration will include a 42-day Screening Period, a 28-week open-label (OL) 40 mg adalimumab eow treatment period (Period 1), a 40 week double-blind placebo controlled eow treatment period (Period 2) with an opportunity to receive at least 12 weeks of rescue therapy (subjects that flare at Weeks 60, 64 or 68 will be allowed 12 weeks of rescue therapy and final visits will be 72, 76 or 80 respectively), plus a 70-day follow-up phone call.

Figure 1. Study Design Schematic
First and second table note previously read:

* Subjects who meet remission criteria (ASDAS inactive disease < 1.3) at Weeks 16, 20, 24 and 28 will be randomized to Period 2. Subjects not meeting remission criteria will be discontinued at Weeks 20, 24 or 28.

** Subjects who flare (ASDAS ≥ 2.1 for 2 consecutive study visits) during the double-blind period (Period 2) can receive rescue therapy with OL ADA 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of this study. The earliest time a subject can meet the flare criteria would be at Week 36 since a subject would need to have 2 consecutive visits with ASDAS ≥ 2.1. Subjects who flare at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80 respectively.

Has been changed to read:

* Subjects who meet remission criteria (ASDAS inactive disease < 1.300) at Weeks 16, 20, 24 and 28 will be randomized to Period 2. Subjects not meeting remission criteria will be discontinued at Weeks 20, 24 or 28.

** Subjects who flare (ASDAS ≥ 2.100 for 2 consecutive study visits) during the double-blind period (Period 2) can receive rescue therapy with OL ADA 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of this study. The earliest time a subject can meet the flare criteria would be at Week 36 since a subject would need to have 2 consecutive visits with ASDAS ≥ 2.100. Subjects who flare at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80 respectively.

Section 5.1 Overall Study Design and Plan: Description
Subsection Screening Period
First paragraph previously read:

Within 30 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.

Has been changed to read:

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.

Section 5.1 Overall Study Design and Plan: Description
Subsection Screening Period
Third paragraph, seventh and eight sentence previously read:

If the subject had completed initial screening evaluation assessments including a purified protein derivative (PPD) test or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-tube test or T SPOT TB test), chest x-ray (CXR), MRI of the SI joints and spine, AP pelvis x-ray, HLA-B27, or electrocardiogram (ECG), these tests will not be required to be repeated for the re-screening provided the conditions noted in Section 5.3 are met and no more than 30 days has passed for the MRI of the SI joints and spine, 3 months (90 days) have passed for the PPD test or IGRA test, CXR and ECG and 1 year

(365 days) for the AP pelvis x-ray. There is no need to redraw the HLA-B27 once the results are available from the central laboratory chosen for this study.

Has been changed to read:

If the subject had completed initial screening evaluation assessments including a purified protein derivative (PPD) test or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-tube test or T SPOT TB test), chest x-ray (CXR), MRI of the SI joints and spine, AP pelvis x-ray, HLA-B27, Antinuclear Antibody (ANA) or electrocardiogram (ECG), these tests will not be required to be repeated for the re-screening provided the conditions noted in Section 5.3 are met and no more than 30 days has passed for the MRI of the SI joints and spine, 3 months (90 days) have passed for the PPD test or IGRA test, CXR and ECG and 1 year (365 days) for the AP pelvis x-ray. There is no need to redraw the HLA-B27 or ANA once the results are available from the central laboratory chosen for this study.

Section 5.1 Overall Study Design and Plan: Description
Subsection <u>Open-Label Period (Period 1)</u>
Third paragraph, last sentence previously read:

At Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

Has been changed to read:

At Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Section 5.1 Overall Study Design and Plan: Description
Subsection Open-Label Period (Period 1)
Fourth paragraph, last sentence previously read:

If the subject does not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

Has been changed to read:

If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Section 5.1 Overall Study Design and Plan: Description
Subsection Open-Label Period (Period 1)
Fifth paragraph, last sentence previously read:

If any of these time points do not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

Has been changed to read:

If any of these time points do not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Section 5.1 Overall Study Design and Plan: Description
Subsection Open-Label Period (Period 1)
Add: new last paragraph

If a subject has an elevated hs-CRP which the investigator believes to be secondary to an AE and not due to nr-axSpA at Weeks 16, 20, 24 or 28, sites may repeat the hs-CRP test prior to the subject's next scheduled visit following a discussion with the AbbVie Medical Monitor. The repeat hs-CRP results should be available to the site prior to the subject's next scheduled visit and will replace the visit-specific hs-CRP in the ASDAS calculation. Instances where AE-related hs-CRP elevation spans more than one study visit will be addressed on a case-by-case basis. *Note: the AE should be reported in EDC prior to discussion with the AbbVie Medical Monitor.*

Section 5.1 Overall Study Design and Plan: Description
Subsection Double-Blind Period (Period 2)
First paragraph, last sentence previously read:

Subjects in remission defined as meeting Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease (ASDAS < 1.3) at Week 16, 20, 24 and Week 28 (described above) will be randomized in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo.

Has been changed to read:

Subjects in remission defined as meeting Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease (ASDAS < 1.300) at Week 16, 20, 24 and Week 28 (described above) will be randomized in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo.

Section 5.1 Overall Study Design and Plan: Description
Subsection Double-Blind Period (Period 2)
Second paragraph, second and third sentence previously read:

Subjects who flare, defined as 2 consecutive study visits with ASDAS ≥ 2.1 in Period 2 (40-week double-blind period) will be allowed rescue therapy. The earliest time a subject can meet the flare criteria would be at Week 36 since a subject would need to have 2 consecutive visits with ASDAS ≥ 2.1.

Has been changed to read:

Subjects who flare, defined as 2 consecutive study visits with ASDAS ≥ 2.100 in Period 2 (40-week double-blind period) will be allowed rescue therapy. The earliest time a subject can meet the flare criteria would be at Week 36 since a subject would need to have 2 consecutive visits with ASDAS ≥ 2.100.

Section 5.1 Overall Study Design and Plan: Description
Subsection Double-Blind Period (Period 2)
Add: new last paragraph

Following the Week 28 visit, if a subject has an elevated hs-CRP which the investigator believes to be secondary to an AE and not due to nr-axSpA, the site may repeat the hs-CRP test prior to the subject's next scheduled visit following a discussion with the AbbVie Medical Monitor. The repeat hs-CRP results should be available to the site prior to the subject's next scheduled visit and will replace the visit-specific hs-CRP in the ASDAS calculation. Instances where AE-related hs-CRP elevation spans more than one study visit will be addressed on a case-by-case basis. *Note: the AE should be reported in EDC prior to discussion with the AbbVie Medical Monitor.*

Section 5.2.1 Inclusion Criteria
Criterion 6 previously read:

Subjects must have baseline disease activity as defined by having an ASDAS ≥ 2.1 (note, sites will need to use the Screening Visit hs-CRP to calculate ASDAS at Screening and Baseline Visits with the remainder of parameters visit-specific), BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits (see Appendix E, Appendix F and Appendix G, respectively).

Has been changed to read:

Subjects must have baseline disease activity as defined by having an ASDAS ≥ 2.100 (note, sites will need to use the Screening Visit hs-CRP to calculate ASDAS at Screening and Baseline Visits with the remainder of parameters visit-specific), BASDAI ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits (see Appendix E, Appendix F and Appendix G, respectively).

Section 5.2.2 Exclusion Criteria
Criterion 4, last sentence previously read:

All other oral DMARDs, with the exception of azathioprine, are prohibited within 28 days prior to the Baseline Visit.

Has been changed to read:

All other oral DMARDs, with the exception of azathioprine or mercaptopurine (6-MP), are prohibited within 28 days prior to the Baseline Visit.

Section 5.2.2 Exclusion Criteria
Criterion 5 previously read:

If entering the study on concomitant azathioprine (AZA), subject not on stable dose (≤ 150 mg per day) for 28 days prior to the Baseline Visit or is on AZA and another concomitant immunosuppressive drug at study entry.

Has been changed to read:

If entering the study on concomitant azathioprine (AZA) or 6-MP, subject not on stable dose (AZA ≤ 150 mg per day or 6-MP ≤ 75 mg per day) for 28 days prior to the Baseline Visit or is on AZA or 6-MP and another concomitant immunosuppressive drug at study entry.

Section 5.2.2 Exclusion Criteria
Criterion 9 previously read:

Subject has received cyclosporine or other second line anti-rheumatic therapy (except MTX, SSZ, hydroxychloroquine or AZA) within 28 days prior to the Baseline Visit.

Has been changed to read:

Subject has received cyclosporine or other second line anti-rheumatic therapy (except MTX, SSZ, hydroxychloroquine, AZA or 6-MP) within 28 days prior to the Baseline Visit.

Section 5.2.3.2 Concomitant Therapy
Third paragraph, first sentence previously read:

Subjects may continue on stable doses of MTX, SSZ, hydroxychloroquine, AZA, prednisone and/or NSAIDs provided the stability requirements noted in Section 5.2.2 are met.

Has been changed to read:

Subjects may continue on stable doses of MTX, SSZ, hydroxychloroquine, AZA, 6-MP, prednisone and/or NSAIDs provided the stability requirements noted in Section 5.2.2 are met.

Section 5.2.3.2 Concomitant Therapy
Second paragraph, last bullet previously read:

- AZA (≤ 150 mg per day)

Has been changed to read:

- AZA (≤ 150 mg per day) or 6-MP (≤ 75 mg per day)

Section 5.2.3.3 Prohibited Therapy
Fourth and fifth bullet previously read:

- All oral DMARDs other than MTX, SSZ, AZA or hydroxychloroquine.
- Opioid analgesics (other than tramadol) or marijuana.

Has been changed to read:

- All oral DMARDs other than MTX, SSZ, AZA, 6-MP or hydroxychloroquine.
- Opioid analgesics (other than tramadol) or marijuana, except as medically indicated for an AE.

Section 5.2.3.4 Rescue Therapy
First paragraph, second sentence previously read:

Flare is defined as 2 consecutive study visits with ASDAS ≥ 2.1.

Has been changed to read:

Flare is defined as 2 consecutive study visits with ASDAS ≥ 2.100.

Section 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart
First paragraph previously read:

Subjects will be allowed a visit window of ±7 days for all study visits (with the exception of the Baseline Visit as there is a maximum of 30 days screening window).

Has been changed to read:

Subjects will be allowed a visit window of ±7 days for all study visits (with the exception of the Baseline Visit as there is a maximum of 42 days screening window).

Table 1. Study Activities
Previously read:

Activity	SCR (<30 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Informed Consent	X																									
Inclusion/ Exclusion Criteria	X	X[b]																								
Medical/ Surgical History	X	X[b]																								
Vital Signs/ Weight/ Height[c]	X	X	X	X	X	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	X		X	X	X	X	
Physical Exam	X	X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
12-Lead ECG[d]	X[e]																									
Chest X-Ray[d]	X[e]															X[f]										
AP Pelvis X-Ray	X[e]																									

Activity	SCR (<30 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
TB Screening (PPD Skin Test OR QuantiFERON-TB Gold Test)	X[e]															X[f]										
Pregnancy Test	X[g]	X[h]						X[h,v]	X[h,v]	X[h,v]										X[h]		X[h,v]	X[h,v]	X[h]	X[h]	
Chemistry and Hematology	X	X[i]		X	X	X	X	X	X	X		X		X		X				X		X[v]	X[v]	X	X	
Urinalysis[j]	X	X[i]				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
HLA-B27	X[e]																									
Antinuclear Antibody (ANA)/ reflex Anti-dsDNA antibody	X																									
HBV Screening	X																									
hs-CRP	X	X[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
HIV	X[k]																									

Activity	SCR (<30 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Biomarkers (DKK-1, Sclerostin, BMP 2, and/or BMP-7)[l]		X						X[v]	X[v]	X			X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
Serum ADA Concentration[l]		X				X		X[v]	X[v]	X		X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
Anti-ADA antibody (AAA)[l]		X				X		X[v]	X[v]	X		X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
PG Sample		X[m]																								
MRI of the Spine and SI Joints	X[e]							X[n]	X[n]	X[n]																
TJC/SJC		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
$BASMI_{lin}$		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
MASES		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	

Activity	SCR (<30 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Plantar Fascia Enthesitis		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
Dactylitis		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
BASFI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Physician's Global Assessment of Disease Activity NRS		X	X	X	X	X	X	X	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	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	X	X	X	X		X	X	X	X	
Patient's Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	

Activity	SCR (<30 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Patient's Global Assessment of Pain NRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
HAQ-S		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
SF-36V2 Health Survey		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
WPAI- axial SpA		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
EQ-5D		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
Prior and Concomitant Therapy Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Monitor AE	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X[p]
ASDAS Calculation	X	X						X[q]	X[q]	X[q]		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]						
Enrollment		X																								
Randomization										X[q]																

Activity	SCR (<30 D)	BL[a] (D1)	Open-Label - Period 1 Week 2	4	8	12	16	20	24	28	Double-Blind – Period 2 Week 32	36	40	44	48	52	56	60	64	68	12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u] 72	76	80	Disc. Visit[x]	70-Day F/U Call
Dispense Study Drug		X		X	X	X	X	X	X	X[q]	X	X	X	X	X	X	X	X	X	X[s]		X[s]	X[s]			
Admin of Study Drug[t]		X	X	X	X	X			X																	

Ada = Adalimumab; BL = Baseline; D = Day(s); Disc Visit = Discontinuation Visit; SCR = Screening; RT = Rescue Therapy; PF = Post Flare; F/U = Follow-up

a. Baseline Visit is defined as Day 1, the day of first study drug administration.

b. Medical History and Inclusion/Exclusion Criteria must be confirmed by the Investigator prior to enrollment to verify subject eligibility.

c. Height will be measured at Screening Visit only.

d. Subject can have a repeat CXR and/or ECG at any time during the study only if in the opinion of the investigator, clinically significant AEs develop that warrant a repeat exam.

e. These procedures will not be required if the subject had a previous normal CXR, normal ECG or negative PPD 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 or AP Pelvis x-ray will also not be required if the subject had a previous test within 30 days and 1 year (365 days) of Screening, respectively. Any documentation of past positive PPD results may be acceptable; however, negative PPD test done more than 90 days prior to the Screening visit will need to be repeated. If the subject has a positive PPD test or IGRA test, has had a past ulcerative reaction to PPD placement and/or a CXR consistent with prior TB exposure, the subject will be required to initiate and complete at least the first 2 weeks (or per local guidelines, whichever is longer) of the prescribed TB prophylaxis, or have documented completion of a full course of TB prophylaxis prior to Baseline (Section 5.3.1.1). There is no need to redraw the HLA-B27 once the results are available from the central laboratory chosen for this study.

f. An annual PPD/QuantiFERON-TB Gold test will be required for those subjects with a negative TB test at Screening. If the annual PPD/QuantiFERON-TB Gold test is positive, a CXR must be performed, the investigator must contact the study designated physician to review the individual data and agree on a decision whether or not additional evaluation is needed.

g. All females of childbearing potential will have a serum pregnancy test at Screening that is performed at the central laboratory.

h. All females of childbearing potential will have a urine pregnancy test performed at Baseline prior to study enrollment and at study discontinuation/completion. The urine pregnancy kit supplies will be provided to the sites via the central laboratory (where allowed by local guidelines). Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study.

i. Laboratory assessments (chemistry, hematology, hs-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 by the central laboratory 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. If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to HIV, and document that the test has been performed. The testing is to be done at a local laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

l. Flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.1. Subjects that flare during the double-blind period (Period 2) will need the following assessments during the visit that flare was determined as well as 12 weeks following the determination of the flare: biomarkers, which may include the following: (Dickkopf-1 [DKK-1], Sclerostin, Bone Morphogenetic Protein [BMP]-2, BMP-7), serum adalimumab and AAA (refer to Section 5.3.2 for further information). These assessments are in addition to the regularly scheduled assessments outlined in the Table above.

m. The pharmacogenic (PG) sample is optional. A separate PG consent form must be signed prior to sample collection. The PG sample is ideally collected at Baseline, but may be collected at anytime throughout the study.

n. Site staff should schedule the Week 28 MRI during the Baseline visit, if possible. For subjects that are discontinued due to not fulfilling the ASDAS remission criteria at Weeks 20 or 24, the site should attempt to reschedule the MRI within 2 weeks of the discontinuation visit. If the MRI cannot be rescheduled, the Week 28 MRI will be considered missed.

o. SAEs will be collected starting from time of signing informed consent; non-serious AEs will be collected starting from the 1st study drug dose. Any SAE that occurs between Screening and Baseline should be captured as medical history.

p. Site personnel will contact all subjects 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.

q. Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued. At Week 24, calculation of the Week 20 ASDAS will be done using the Week 20 visit parameters including the Week 20 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued. At Week 28, calculation of the Week 24 ASDAS will be done using the Week 24 parameters including the Week 24 hs-CRP; the Week 28 ASDAS will be done using Week 28 parameters and the Week 24 hs-CRP (as the Week 28 results will not be available). If any of these time points do not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

r. Beginning at Week 36, ASDAS will be calculated via IVRS/IWRS for the current and previous study visit to determine fulfillment of flare criteria. Assessments from the current and previous study visit will be used for the calculation except for the hs-CRP which will be based on the results from the previous study visit's blood draw for both calculations. For subjects who meet flare criteria during Period 2 and start rescue therapy with OL adalimumab, further calculation of ASDAS is not required. For any subject missing 2 consecutive visits within the double-blind period (Period 2) the site must contact the AbbVie Medical Monitor for discussion regarding the subject's continued participation in the study.

s. Subjects would only receive study drug at Weeks 68, 72 or 76, if they flared at Week 56, 60 or 64 respectively.

t. Study drug will be administered in the Investigator's office at Baseline, Week 2, 4, 8, 12, and Week 24 to ensure proper technique.

u. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

v. These procedures should only be performed if the visit is the subject's last visit due to not meeting ASDAS remission criteria (Weeks 20, 24 or 28) or due to a flare and has received 12 weeks of rescue therapy (Weeks 72 or 76).

w. If subject meets flare criteria, these assessments are required 12 weeks post flare in addition to assessments for the scheduled visit when the flare was identified. If any of these procedures are already collected at the regularly scheduled visit, there is no need to obtain these procedures twice.

x. Subjects who prematurely discontinue the study should complete the procedures outlined for the Discontinuation Visit as soon as possible after the last dose of study drug and preferably prior to the administration of new therapies. No Discontinuation Visit procedures will be required for those subjects that complete the Week 68 visit (or Weeks 72, 76 or 80 for those subjects who flare at Weeks 60, 64 or 68, respectively).

Has been changed to read:

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Informed Consent	X																									
Inclusion/ Exclusion Criteria	X	X[b]																								
Medical/ Surgical History	X	X[b]																								
Vital Signs/ Weight/ Height[c]	X	X	X	X	X	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	X		X	X	X	X	
Physical Exam	X	X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
12-Lead ECG[d]	X[e]																									
Chest X-Ray[d]	X[e]															X[f]										
AP Pelvis X-Ray	X[e]																									

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
TB Screening (PPD Skin Test OR IGRA)	X[e]															X[f]										
Pregnancy Test	X[g]	X[h]						X[h,v]	X[h,v]	X[h,v]										X[h]		X[h,v]	X[h,v]	X[h]	X[h]	
Chemistry and Hematology	X	X[i]		X	X	X	X	X	X	X		X		X		X				X		X[v]	X[v]	X	X	
Urinalysis[j]	X	X[i]				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
HLA-B27	X[e]																									
Antinuclear Antibody (ANA)/ reflex Anti-dsDNA antibody	X[e]																									
HBV Screening	X																									
hs-CRP	X	X[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
HIV	X[k]																									

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Biomarkers[l]		X						X[v]	X[v]	X		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
Serum ADA Concentration[l]		X				X		X[v]	X[v]	X		X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
Anti-ADA antibody (AAA)[l]		X				X		X[v]	X[v]	X		X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[v]	X[v]	X	X	
PG Sample		X[m]																								
MRI of the Spine and SI Joints	X[e]							X[n]	X[n]	X[n]																
TJC/SJC		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
$BASMI_{lin}$		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
MASES		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Plantar Fascia Enthesitis		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
Dactylitis		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
BASFI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Physician's Global Assessment of Disease Activity NRS		X	X	X	X	X	X	X	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	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	X	X	X	X		X	X	X	X	
Patient's Global Assessment of Disease Activity NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Patient's Global Assessment of Pain NRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
HAQ-S		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
SF-36V2 Health Survey		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
WPAI- axial SpA		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
EQ-5D		X				X		X[v]	X[v]	X		X				X				X		X[v]	X[v]	X	X	
Prior and Concomitant Therapy Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Monitor AE	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X[p]
ASDAS Calculation	X	X						X[q]	X[q]	X[q]		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]						
Enrollment		X																								
Randomization										X[q]																

Activity	SCR (≤42 D)	BL[a] (D1)	Open-Label - Period 1								Double-Blind – Period 2										12 Weeks PF[w]	RT for Those that Flare at Week 60–68[u]			Disc. Visit[x]	70-Day F/U Call
			Week								Week															
			2	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68		72	76	80		
Dispense Study Drug		X		X	X	X	X	X	X	X[q]	X	X	X	X	X	X	X	X	X	X[s]		X[s]	X[s]			
Admin of Study Drug[t]		X	X	X	X	X			X																	
Optional Blood Sample Collection Sub-Study		X						X[y]	X[y]	X		X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]						

Ada = Adalimumab; BL = Baseline; D = Day(s); Disc Visit = Discontinuation Visit; SCR = Screening; RT = Rescue Therapy; PF = Post Flare; F/U = Follow-up

a. Baseline Visit is defined as Day 1, the day of first study drug administration.

b. Medical History and Inclusion/Exclusion Criteria must be confirmed by the Investigator prior to enrollment to verify subject eligibility.

c. Height will be measured at Screening Visit only.

d. Subject can have a repeat CXR and/or ECG at any time during the study only if in the opinion of the investigator, clinically significant AEs develop that warrant a repeat exam.

e. These procedures will not be required if the subject had a previous normal CXR, normal ECG or negative PPD 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 or AP Pelvis x-ray will also not be required if the subject had a previous test within 30 days and 1 year (365 days) of Screening, respectively. Any documentation of past positive PPD results may be acceptable; however, negative PPD test done more than 90 days prior to the Screening visit will need to be repeated. If the subject has a positive PPD test or IGRA test, has had a past ulcerative reaction to PPD placement and/or a CXR consistent with prior TB exposure, the subject will be required to initiate and complete at least the first 2 weeks (or per local guidelines, whichever is longer) of the prescribed TB prophylaxis, or have documented completion of a full course of TB prophylaxis prior to Baseline (Section 5.3.1.1). There is no need to redraw the HLA-B27 or ANA once the results are available from the central laboratory chosen for this study.

f. An annual PPD/IGRA test will be required for those subjects with a negative TB test at Screening. If the annual PPD/IGRA test is positive, a CXR must be performed, the investigator must contact the study designated physician to review the individual data and agree on a decision whether or not additional evaluation is needed.

g. All females of childbearing potential will have a serum pregnancy test at Screening that is performed at the central laboratory.

h. All females of childbearing potential will have a urine pregnancy test performed at Baseline prior to study enrollment and at study discontinuation/completion. The urine pregnancy kit supplies will be provided to the sites via the central laboratory (where allowed by local guidelines). Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study.

i. Laboratory assessments (chemistry, hematology, hs-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 by the central laboratory 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. If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to HIV, and document that the test has been performed. The testing is to be done at a local laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

l. Flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.100. Subjects that flare during the double-blind period (Period 2) will need the following assessments during the visit that flare was determined as well as 12 weeks following the determination of the flare: biomarkers (refer to Section 5.3.1.1 for further information), serum adalimumab and AAA (refer to Section 5.3.2 for further information). These assessments are in addition to the regularly scheduled assessments outlined in the table above.

m. The pharmacogenic (PG) sample is optional. A separate PG consent form must be signed prior to sample collection. The PG sample is ideally collected at Baseline, but may be collected at any time throughout the study.

n. Site staff should schedule the Week 28 MRI during the Baseline visit, if possible. For subjects that are discontinued due to not fulfilling the ASDAS remission criteria at Weeks 20 or 24, the site should attempt to reschedule the MRI within 2 weeks (14 days) of the discontinuation visit. If the MRI cannot be rescheduled, the Week 28 MRI will be considered missed.

o. SAEs will be collected starting from time of signing informed consent; non-serious AEs will be collected starting from the 1st study drug dose. Any AE that occurs between Screening and Baseline should be captured as medical history.

p. Site personnel will contact all subjects 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.

q. Week 20, calculation of the Week 16 ASDAS will be done using the Week 16 visit parameters including the Week 16 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued. At Week 24, calculation of the Week 20 ASDAS will be done using the Week 20 visit parameters including the Week 20 hs-CRP. If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued. At Week 28, calculation of the Week 24 ASDAS will be done using the Week 24 parameters including the Week 24 hs-CRP; the Week 28 ASDAS will be done using Week 28 parameters and the Week 24 hs-CRP (as the Week 28 results will not be available). If any of these time points do not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued. For hs-CRP elevations secondary to AEs or using a previous hs-CRP, please refer to Section 5.1 or ASDAS Calculation in Section 5.3.1.1.

r. Beginning at Week 36, ASDAS will be calculated via IVRS/IWRS for the current and previous study visit to determine fulfillment of flare criteria. Assessments from the current and previous study visit will be used for the calculation except for the hs-CRP which will be based on the results from the previous study visit's blood draw for both calculations. For subjects who meet flare criteria during Period 2 and start rescue therapy with OL adalimumab, further calculation of ASDAS is not required. For any subject missing 2 consecutive visits within the double-blind period (Period 2) the site must contact the AbbVie Medical Monitor for discussion regarding the subject's continued participation in the study.

s. Subjects would only receive study drug at Weeks 68, 72 or 76, if they flared at Week 56, 60 or 64 respectively.

t. Study drug will be administered in the Investigator's office at Baseline, Week 2, 4, 8, 12, and Week 24 to ensure proper technique.

u. For subjects who meet the flare criteria at Weeks 60, 64 or 68, rescue therapy with OL adalimumab will be provided for 12 weeks and final study visit will be at Weeks 72, 76 or 80, respectively.

v. These procedures should only be performed if the visit is the subject's last visit due to not meeting ASDAS remission criteria (Weeks 20, 24 or 28) or due to a flare and has received 12 weeks of rescue therapy (Weeks 72 or 76).

w. If subject meets flare criteria, these assessments are required 12 weeks post flare in addition to assessments for the scheduled visit when the flare was identified. If any of these procedures are already collected at the regularly scheduled visit, there is no need to obtain these procedures twice.

x. Subjects who prematurely discontinue the study should complete the procedures outlined for the Discontinuation Visit as soon as possible after the last dose of study drug and preferably prior to the administration of new therapies. No Discontinuation Visit procedures will be required for those subjects that complete the Week 68 visit (or Weeks 72, 76 or 80 for those subjects who flare at Weeks 60, 64 or 68, respectively).

y. Optional Blood Sample Collection Sub-Study only: use a separate sub-study central lab kit. Samples will be collected at Week 28 or at Weeks 20 or 24 only if the visit is the subject's last visit. (Optional Blood Sample Collection Sub-Study samples are in addition to the regularly scheduled assessments outlined in the table above.)

z. Optional Blood Sample Collection Sub-Study only: use a separate sub-study central lab kit. In subjects who meet flare criteria during Weeks 36 – 68, samples will be collected only once at time of flare. Flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.100. (Optional Blood Sample Collection Sub-Study samples are in addition to the regularly scheduled assessments outlined in the Table above.)

Section 5.3.1.1 Study Procedures
Subsection Chest X-Ray (CXR)
Last paragraph previously read:

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

Has been changed to read:

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.

Section 5.3.1.1 Study Procedures
Subsection Anteroposterior Pelvis X-ray
Fourth paragraph, fifth and sixth sentence previously read:

The imaging vendor will complete an imaging worksheet and return an eligibility notification report to the site within 48 hours of imaging vendor's receipt of the films (or within 96 hours if adjudication is necessary). The investigator will be required to review, sign and date the eligibility notification report.

Has been changed to read:

The imaging vendor will complete an imaging worksheet and return an eligibility notification report to the site within 48 hours of imaging vendor's receipt of the films (or within 96 hours if adjudication is necessary), not including BioClinica holidays or weekends. The investigator will be required to review, sign and date the eligibility notification report prior to the subject being enrolled.

Section 5.3.1.1 Study Procedures
Subsection TB Screening
Sixth paragraph, first and second sentence previously read:

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

Has been changed to read:

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.

Section 5.3.1.1 Study Procedures
Subsection ANA
Add: new subsection

ANA

Testing for ANA will be performed on specimens collected during the Screening visit. For subjects that may need to be rescreened, once results are available from the central laboratory chosen for this study repeat ANA testing is not required.

Section 5.3.1.1 Study Procedures
Subsection Biomarkers
First paragraph, last sentence previously read:

The samples collected may include the following:

Has been changed to read:

The final set of biomarkers to be analyzed may include the following:

Section 5.3.1.1 Study Procedures
Subsection Biomarkers
Add: new second paragraph

The final selection of biomarkers for analysis will be based on both insights gained in the sub-study and available scientific knowledge at study completion.

Section 5.3.1.1 Study Procedures
Subsection Biomarkers
Delete: fourth sentence in second paragraph

Results of exploratory analyses, if any, will not be reported with the study summary.

Section 5.3.1.1 Study Procedures
Subsection Biomarkers
Second paragraph, last sentence previously read:

The samples will be retained for no longer than 5 years after completion of the study (where allowed by local guidelines).

Has been changed to read:

The samples will be retained for no longer than 5 years after completion of the study defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

Section 5.3.1.1 Study Procedures
Subsection Biomarkers
Add: new last paragraph

Biomarker analyses are considered exploratory. Results for the primary biomarker analyses from the overall study and sub-study will be reported in a separate biomarker study report. The primary biomarker analyses do not preclude future analyses which are not within the scope of this study protocol and will therefore not be included in the separate biomarker study report.

Section 5.3.1.1 Study Procedures
Subsection MRI of the Spine and Sacroiliac Joints
Third paragraph, last sentence previously read:

The investigator will be required to review, sign and date the eligibility notification report.

Has been changed to read:

The investigator will be required to review, sign and date the eligibility notification report prior to the subject being enrolled.

Section 5.3.1.1 Study Procedures
Subsection MRI of the Spine and Sacroiliac Joints
Last paragraph, second and third sentence previously read:

For subjects that are discontinued due to not fulfilling the ASDAS remission criteria at Weeks 20 or 24, the site should attempt to reschedule the MRI within 2 weeks of the discontinuation visit. If the MRI cannot be rescheduled, the Week 28 MRI will be considered missed.

Has been changed to read:

For subjects that are discontinued for any reason at Weeks 20, 24 or 28, the site should attempt to reschedule the MRI within 2 weeks (14 days) of the discontinuation visit. If the MRI cannot be rescheduled within 14 days of the discontinuation visit, the Week 28 MRI will be considered missed.

Section 5.3.1.1 Study Procedures
Subsection Numerical Rating Scales (NRS)
First bullet, first sub-bullet, second sentence previously read:

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

Has been changed to read:

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.

Section 5.3.1.1 Study Procedures
Subsection Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation
First paragraph, fourth sentence previously read:

If the subject does not meet the criteria of an ASDAS ≥ 2.1 at screening, the subject would be considered a screen failure and all other screening procedures should be cancelled.

Has been changed to read:

If the subject does not meet the criteria of an ASDAS ≥ 2.100 at screening, the subject would be considered a screen failure and all other screening procedures should be cancelled.

Section 5.3.1.1 Study Procedures
Subsection Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation
Third paragraph, last sentence previously read:

If the subject does not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

Has been changed to read:

If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Section 5.3.1.1 Study Procedures
Subsection Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation
Fourth paragraph, last sentence previously read:

If the subject does not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

Has been changed to read:

If the subject does not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Section 5.3.1.1 Study Procedures
Subsection Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation
Fifth paragraph, last sentence previously read:

If any of these time points do not meet the criteria for remission (ASDAS < 1.3), the subject will be discontinued.

Has been changed to read:

If any of these time points do not meet the criteria for remission (ASDAS < 1.300), the subject will be discontinued.

Section 5.3.1.1 Study Procedures
Subsection Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation
Eighth paragraph, second sentence previously read:

Starting at Week 36 through Week 68, subjects will be assessed for flare, defined as 2 consecutive visits with ASDAS ≥ 2.1.

Has been changed to read:

Starting at Week 36 through Week 68, subjects will be assessed for flare, defined as 2 consecutive visits with ASDAS ≥ 2.100.

Section 5.3.1.1 Study Procedures
Subsection Ankylosing Spondylitis Disease Activity Score (ASDAS) Calculation
Add: new tenth paragraph

If a subject has an elevated hs-CRP which the investigator believes to be secondary to an AE and not due to nr-axSpA, sites may repeat the hs-CRP test prior to the subject's next scheduled visit following a discussion with the AbbVie Medical Monitor. The repeat hs-CRP results should be available to the site prior to the subject's next scheduled visit

and will replace the visit-specific hs-CRP in the ASDAS calculation. Instances where AE-related hs-CRP elevation spans more than one study visit will be addressed on a case-by-case basis. *Note: the AE should be reported in EDC prior to discussion with the AbbVie Medical Monitor.*

Section 5.3.1.1 Study Procedures
Subsection Randomization
First sentence previously read:

During the Week 28 visit, subjects meeting ASDAS Inactive Disease (ASDAS < 1.3) at Weeks 16, 20, 24 and 28 will be randomized using IVRS/IWRS in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo.

Has been changed to read:

During the Week 28 visit, subjects meeting ASDAS Inactive Disease (ASDAS < 1.300) at Weeks 16, 20, 24 and 28 will be randomized using IVRS/IWRS in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo.

Section 5.3.1.1 Study Procedures
Subsection Optional Blood Sample Collection Sub-Study
Add: new subsection

Optional Blood Sample Collection Sub-Study

An Optional Blood Sample Collection Sub-Study for future research (separate from the blood sample collection listed above) will be offered to approximately 10 sites based on interest, ongoing enrollment and clinical trial conduct. Samples will be obtained for the Optional Blood Sample Collection Sub-Study at up to three time points (baseline, remission/Week 28 [Weeks 20 or 24 if the subject's last visit], and at time of flare, if applicable). Timing of blood samples to be obtained are outlined in the designated study visits in Table 1 and described in more detail within the "Optional Blood Sample Collection Sub-Study Guidelines," which will be sent separately to the approved sub-study sites.

Section 5.3.2 Drug Concentration Measurements
Section title previously read:

Drug Concentration Measurements

Has been changed to read:

Drug Concentration, Pharmacogenic, and Biomarker Measurements

Section 5.3.2 Drug Concentration Measurements
Second paragraph previously read:

Blood samples for biomarker analysis will be collected at Baseline, Week 28, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit.

Has been changed to read:

Blood samples for biomarker analysis will be collected at Baseline, Weeks 28, 68, time of flare (if applicable), 12 weeks post flare (if applicable), and last study visit.

Section 5.3.2 Drug Concentration Measurements
Add: new last paragraph

Sites approved for the Optional Blood Sample Collection Sub-Study should refer to the "Optional Blood Sample Collection Sub-Study Guidelines" for collection, handling/processing, storage and disposition of samples.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection <u>Biomarker Analysis</u>
Delete: fourth sentence in second paragraph

Results of exploratory analyses, if any, will not be reported with the study summary.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Biomarker Analysis
Second paragraph, last sentence previously read:

The samples will be retained for no longer than 5 years after completion of the study (where allowed by local guidelines).

Has been changed to read:

The samples will be retained for no longer than 5 years after completion of the study defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

Section 5.3.2.2 Handling/Processing of Samples
Subsection Biomarker Analysis
Second paragraph, last sentence previously read:

The samples will be retained for no longer than 5 years after completion of the study (where allowed by local guidelines).

Has been changed to read:

The samples will be retained for no longer than 5 years after completion of the study defined as the date of the last subject's last study visit or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

Section 5.3.2.2 Handling/Processing of Samples
Subsection Pharmacogenetic Analysis
Third paragraph, last sentence previously read:

The samples will be retained while research on adalimumab (or drugs of this class) continues but no longer than 5 years (where allowed by local guidelines).

Has been changed to read:

The samples will be retained while research on adalimumab (or drugs of this class) continues but no longer than 5 years defined as the date of the last subject's last study visit

or the actual date of follow-up contact, whichever is later (where allowed by local guidelines).

Section 5.3.2.4 Measurement Methods
Previously read:

Serum concentrations of adalimumab, AAA and biomarkers will be determined using validated ligand binding methods under the supervision of the Drug Analysis Department at AbbVie.

Has been changed to read:

Serum concentrations of adalimumab and AAA will be determined using validated ligand binding methods under the supervision of the Drug Analysis Department at AbbVie.

Section 5.3.3.1 Primary Efficacy Variable
Previously read:

The primary efficacy variable is the proportion of subjects who do not experience a flare during Period 2 by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS ≥ 2.1.

Has been changed to read:

The primary efficacy variable is the proportion of subjects who do not experience a flare during Period 2 by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS ≥ 2.100.

Section 5.3.3.2 Secondary Efficacy Variable(s)
Subsection <u>At 12 Weeks after Initiation of Rescue Therapy</u>
First, second and third bullet previously read:

- ASDAS Inactive Disease (ASDAS < 1.3)
- ASDAS Major Improvement (a change from baseline ≤ –2.00)
- ASDAS Clinically Important Improvement (a change from baseline ≤ –1.10)

Has been changed to read:

- ASDAS Inactive Disease (ASDAS < 1.300)
- ASDAS Major Improvement (a change from baseline ≤ –2.000)
- ASDAS Clinically Important Improvement (a change from baseline ≤ –1.100)

Section 5.3.3.2 Secondary Efficacy Variable(s)
Subsection <u>At Week 68</u>
First and second bullet previously read:

- Time to flare defined as ASDAS ≥ 2.1 at 2 consecutive visits
- Time to partial flare defined as ASDAS ≥ 1.3 but < 2.1 at 2 consecutive visits

Has been changed to read:

- Time to flare defined as ASDAS ≥ 2.100 at 2 consecutive visits
- Time to partial flare defined as ASDAS ≥ 1.300 but < 2.100 at 2 consecutive visits

Section 5.3.3.3 Other Efficacy Variables
Previously read:

5.3.3.3 Other Efficacy Variables

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of Total back pain
- Bath AS Functional Index (BASFI)
- Inflammation/Morning Stiffness (mean of BASDAI questions 5 and 6)
- Bath AS Disease Activity Index (BASDAI)
- ASDAS
- hs-CRP
- Linear Bath AS Metrology Index ($BASMI_{lin}$)
- Swollen Joint Count (66 joints)
- Tender Joint Count (68 joints)

- MASES
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Pain
- Patient's Assessment of Nocturnal Back Pain
- Anterior Uveitis
- Short Form-36v2 Health Survey questionnaire
- EQ-5D
- WPAI-axial SpA
- SPARCC scores for MRI of the SI joint and spine
- Proportion of subjects who regain remission on rescue therapy
- Time to regain remission on rescue therapy

Each subject will have blood drawn for Biomarkers at the following time points: Baseline, Week 28, time of flare, 12 weeks following determination of flare, and last study visit. The biomarkers may include the following:

- DKK-1
- Sclerostin
- BMP-2
- BMP-7

Has been changed to read:

5.3.3.3 Other Efficacy Variables

- Patient's Global Assessment of Disease Activity
- Patient's Assessment of Total back pain
- Bath AS Functional Index (BASFI)
- Inflammation/Morning Stiffness (mean of BASDAI questions 5 and 6)

- Bath AS Disease Activity Index (BASDAI)
- ASDAS
- hs-CRP
- Linear Bath AS Metrology Index ($BASMI_{lin}$)
- Swollen Joint Count (66 joints)
- Tender Joint Count (68 joints)
- MASES
- Plantar fascia enthesitis
- Dactylitis
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Pain
- Patient's Assessment of Nocturnal Back Pain
- Anterior Uveitis
- Short Form-36v2 Health Survey questionnaire
- EQ-5D
- WPAI-axial SpA
- SPARCC scores for MRI of the SI joint and spine
- Proportion of subjects who regain remission on rescue therapy
- Time to regain remission on rescue therapy

5.3.3.4 Exploratory Variables

Each subject will have blood drawn for Biomarkers at the following time points: Baseline, Weeks 28, 68, time of flare, 12 weeks following determination of flare, and last study visit. The final set of biomarkers to be analyzed may include the following:

- DKK-1
- Sclerostin
- BMP-2
- BMP-7

The final selection of biomarkers for analysis will be based on both insights gained in the sub-study and available scientific knowledge at study completion.

Section 5.3.5 Safety Variables
Last sentence previously read:

The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, physical examination (if required) and laboratory tests.

Has been changed to read:

The following safety evaluations will be performed during the study: concomitant medication review, AE monitoring, vital signs, physical examination (if required) and laboratory tests.

Section 5.5.1 Treatments Administered
Subsection Rescue Therapy During Period 2
First sentence previously read:

Starting at Week 36, subjects who meet the flare criteria (flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.1) will be given rescue therapy with open-label adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study.

Has been changed to read:

Starting at Week 36, subjects who meet the flare criteria (flare is defined as 2 consecutive study visits with ASDAS $\geq$ 2.100) will be given rescue therapy with open-label adalimumab 40 mg eow for at least 12 weeks and will continue through the duration of the subject's participation of the study.

Section 5.5.2.2 Storage and Disposition of Study Drug
Second paragraph previously read:

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Has been changed to read:

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 local guidelines and a well-documented procedure is in place) or returned to AbbVie or third party drug destruction depot.

Section 5.6.3 Suitability of Subject Population
Previously read:

Males and females at least 18 years of age with nr-axSpA who have a minimum level of disease activity at baseline (ASDAS ≥ 2.1, BASDAI ≥ 4, Patient's Assessment of Total Back Pain score ≥ 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), have had an inadequate response or intolerance to two or more NSAIDs or have an intolerance to, or a contraindication for NSAIDs, and who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study.

Has been changed to read:

Males and females at least 18 years of age with nr-axSpA who have a minimum level of disease activity at baseline (ASDAS ≥ 2.100, BASDAI ≥ 4, Patient's Assessment of Total Back Pain score ≥ 4), have objective evidence of active disease (inflammation in the SI joints or spine on MRI or elevated hs-CRP), have had an inadequate response or intolerance to two or more NSAIDs or have an intolerance to, or a contraindication for NSAIDs, and who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study.

Section 6.5 Adverse Event Reporting
First paragraph, last sentence previously read:

Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® system or if RAVE is not operable should use the SAE Non-CRF paper forms and send them to Clinical Pharmacovigilance within 24 hours of being made aware of the adverse event.

Has been changed to read:

Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® system or if RAVE is not operable should use the SAE Non-CRF paper forms and send them (email is the preferred route) to Clinical Pharmacovigilance within 24 hours of being made aware of the adverse event.

Section 6.5 Adverse Event Reporting
"Primary Study Designated Physician" contact information previously read:

Has been changed to read:

Section 8.1.2 Statistical and Analytical Plan
Fourth paragraph, first sentence previously read:

An interim database lock is planned when all ongoing subjects have completed Week 28 of the study.

Has been changed to read:

An interim database lock is planned when all ongoing subjects have completed Week 28 (OL, Period 1) of the study.

Section 8.1.4.1.1 Primary Analysis of Primary Efficacy Endpoint
First sentence previously read:

The primary efficacy endpoint is the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study, which defined as having any 2 consecutive study visits with ASDAS $\geq$ 2.1, and the response rate observed in the group randomized to adalimumab 40 mg eow will be compared to that in the placebo group.

Has been changed to read:

The primary efficacy endpoint is the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study, which defined as having any 2 consecutive study

visits with ASDAS ≥ 2.100, and the response rate observed in the group randomized to adalimumab 40 mg eow will be compared to that in the placebo group.

Section 9.3 Subject Information and Consent
Add: new fifth paragraph

Information regarding incentives for subjects and 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.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical
		Pharmacokinetics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Statistics
		Clinical
		Pharmacokinetics

Document Approval

Study M13375 - A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis - Amendment 2 - EudraCT 2012-000646-35 - 15Jan2015

Version: 2.0 **Date:** 21-Jan-2015 03:23:45 PM **Abbott ID:** 01212015-00F9F680B6956E-00002-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	16-Jan-2015 03:50:04 PM	Author
	19-Jan-2015 04:19:44 PM	Approver
	19-Jan-2015 11:29:07 PM	Approver
	20-Jan-2015 10:29:24 PM	Approver
	21-Jan-2015 03:23:39 PM	Approver