

1.0 Title Page

Clinical Study Protocol M16-098

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis

Incorporating Amendment 0.01 (VHP Countries), Amendment 1, Administrative Change 1, Administrative Change 2, and Amendment 2

AbbVie Investigational Product:	Upadacitinib	
Date:	20 December 2019	
Development Phase:	2/3	
Study Design:	A randomized, double-blind, parallel-group, placebo controlled multicenter study	
EudraCT Number:	2017-000431-14	
Investigators:	Multicenter Trial (Investigator information is on file at AbbVie)	
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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	12 April 2017
Amendment 0-01 (VHP Countries)	27 June 2017
Amendment 0-02 (KR Only)	01 September 2017
Amendment 1	12 September 2017
Administrative Change 1	15 December 2017
Administrative Change 2	11 July 2018

The purpose of this amendment is to:

- Apply administrative changes throughout the protocol.
Rationale: Revised text to improve consistency and readability, and/or provide clarification.
- Add: events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. (Section 3.2, Benefits and Risks)
Rationale: To align with the information stated in the most recent version of the upadacitinib Investigator's Brochure.
- Add management of herpes zoster and added recommendation for periodic skin examination for patients who are at increased risk for skin cancer. (Section 6.1.7, Toxicity Management)
Rationale: To align with Rinvoq[®] labeling.
- Add management of thrombosis events. (Section 5.4.1, Discontinuation of Individual Subjects and Section 6.1.7, Toxicity Management)
Rationale: To add an additional safety precaution for subjects, given the recent concerns raised for the JAK inhibitor class regarding venous thromboembolic events.
- Amend language allowing the Investigator to decide if study drug should be restarted if the subject experiences a study drug interruption > 7 consecutive

days during Weeks 1 through 14 (Period 1) or > 30 consecutive days.
(Section 5.5.4, Selection and Timing of Dose for Each Subject)

Rationale: *To provide a mechanism for continuation of study drug after study drug interruption based on Investigator judgment instead of mandatory study drug discontinuation.*

- Update report signatories. ([Appendix B](#), List of Protocol Signatories)

Rationale: *To reflect changes in AbbVie personnel assigned to project.*

An itemized list of all changes made to the protocol under this amendment can be found in [Appendix H](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M16-098
Name of Study Drug: Upadacitinib	Phase of Development: 2/3
Name of Active Ingredient: Upadacitinib	Date of Protocol Synopsis: 20 December 2019
Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis	
Objectives: The primary objectives of the study are: <u>Period 1</u> <ol style="list-style-type: none"> To evaluate the efficacy of upadacitinib compared with placebo on reduction of signs and symptoms as measured by proportion of subjects who achieve an Assessment of SpondyloArthritis international Society (ASAS) 40 response at Week 14 in subjects with active ankylosing spondylitis (AS) who have had an inadequate response to at least two nonsteroidal anti-inflammatory drugs (NSAIDs) or intolerance to or a contraindication for NSAIDs, and who are biologic disease-modifying antirheumatic drug (bDMARD)-naïve. To assess the safety and tolerability of upadacitinib in subjects with active AS who have had an inadequate response to at least two NSAIDs or intolerance to or a contraindication for NSAIDs, and who are bDMARD-naïve. <u>Period 2</u> To evaluate the safety, tolerability, and efficacy of upadacitinib through up to 2 years of treatment in subjects who have completed Period 1.	
Investigators: Multicenter	
Study Sites: Approximately 107 sites worldwide	
Study Population: Adults who have a clinical diagnosis of AS and meet the modified New York Criteria for AS prior to study entry, who have had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or intolerance to or a contraindication for NSAIDs as defined by the Investigator, and who are bDMARD-naïve.	
Number of Subjects to be Enrolled: Approximately 170 subjects	
Methodology: This is a Phase 2/3 multicenter study that includes two periods. Period 1 is a 14-week randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo for the treatment of subjects with active AS who have had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or intolerance to or a contraindication for NSAIDs as defined by the Investigator, and who are bDMARD-naïve. Period 2 is an open-label long-term extension to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with AS who have completed Period 1. The study duration will include a 35-day screening period; a 14-week randomized, double-blind, placebo-controlled period (Period 1); a 90-week open-label extension period (Period 2); and a 30-day follow-up visit.	

Methodology (Continued):

X-ray of the pelvis will be performed within the 35-day screening period to evaluate the sacroiliac (SI) joints to confirm the fulfillment of the modified New York Criteria for AS. X-ray of the spine will also be performed within the 35-day screening period to assess for total spinal ankylosis; subjects with total spinal ankylosis are not eligible for this study. The x-rays of the spine and pelvis will not be required during the Screening Period if the subject had a previous anteroposterior (AP) pelvis x-ray and lateral spine x-rays within 90 days of the Screening Period, provided that the x-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to one of two treatment groups:

- Group 1: Upadacitinib 15 mg QD (n = 85)
- Group 2: Placebo (n = 85)

Randomization will be stratified by Screening high sensitivity C-reactive protein (hsCRP) (\leq upper limit of normal [ULN] vs. $>$ ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

If entering the study on concomitant conventional-synthetic disease modifying antirheumatic drugs (csDMARDs) (i.e., methotrexate [MTX], leflunomide, sulfasalazine [SSZ], and/or hydroxychloroquine), the subject must be on a stable dose for ≥ 4 weeks prior to the first dose of study drug. If entering the study on concomitant oral corticosteroids, subject must be on a stable dose of prednisone (≤ 10 mg/day) or oral corticosteroid equivalents for at least 14 days prior to the first dose of study drug. The dose(s) of csDMARDs and corticosteroids should remain stable throughout the study (except as described for rescue therapy), but may be decreased only for safety reasons.

If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen and codeine or hydrocodone, and/or non-opioid analgesics, subject must be on stable dose(s) for at least 14 days prior to the first dose of study drug and should remain stable throughout the study (except as described for rescue therapy), but may be decreased only for safety reasons.

Starting at Week 16, subjects who do not achieve at least an ASAS 20 response at two consecutive visits will have the option to add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or modify dose of MTX or SSZ at Week 20 or thereafter.

Starting at Week 24, subjects who still do not achieve at least an ASAS 20 response at two consecutive visits will be discontinued from study drug treatment.

Subjects who complete the Week 14 visit (end of Period 1) will enter the open-label long-term extension portion of the study, Period 2 (90 weeks). Subjects who are assigned to upadacitinib in Period 1 will continue to receive upadacitinib in an open-label manner. Subjects who were randomized to placebo at Baseline will also receive open-label upadacitinib 15 mg QD at Week 14.

The primary analysis will be conducted after all subjects have completed Week 14 or have prematurely discontinued prior to Week 14. Study sites and subjects will remain blinded to the treatment assignment in Period 1 for the duration of the study.

Optional samples may be collected for exploratory research at designated time points throughout the study.

Methodology (Continued):

Subjects will have an x-ray of the spine at Week 104. All subjects who meet eligibility criteria will have a magnetic resonance imaging (MRI) evaluation of the sacroiliac (SI) joints, as well as the cervical, thoracic, and lumbar regions of the spine, prior to or at the Baseline Visit, at Week 14, and Week 104.

Subjects at select sites who consent to participate in the low-dose computer tomography (CT) scan substudy and meet eligibility criteria will have low-dose CT scan evaluation of the whole spine (cervical, thoracic, and lumbar spine) prior to or at the Baseline Visit, Week 52, and Week 104.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female ≥ 18 years of age.
2. Subject with a clinical diagnosis of AS and meeting the modified New York Criteria for AS.
3. Subject must have baseline disease activity as defined by having a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 Numeric Rating Scale (NRS) at the Screening and Baseline Visits.
4. Subject has had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses, or subject has an intolerance to or contraindication for NSAIDs as defined by the Investigator.
5. If entering the study on concomitant MTX, leflunomide, SSZ, and/or hydroxychloroquine, subject must be on a stable dose of MTX (≤ 25 mg/week) and/or SSZ (≤ 3 g/day) and/or hydroxychloroquine (≤ 400 mg/day) or leflunomide (≤ 20 mg/day) for at least 28 days prior to the Baseline Visit. A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
6. If entering the study on concomitant oral corticosteroids, subject must be on a stable dose of prednisone (≤ 10 mg/day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
7. If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen and codeine or hydrocodone, and/or non-opioid analgesics, subject must be on stable dose(s) for at least 14 days prior to the Baseline Visit.

Main Exclusion:

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Prior exposure to any biologic therapy with a potential therapeutic impact on spondyloarthritis (SpA).
3. Intra-articular joint injections, spinal/paraspinal injection(s), or parenteral administration of corticosteroids within 28 days prior to the Baseline Visit. Inhaled or topical corticosteroids are allowed.
4. Subject on any other DMARDs (other than those allowed), thalidomide, or apremilast within 28 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit.
5. Subject on opioid analgesics (except for combination acetaminophen/codeine or acetaminophen/hydrocodone which are allowed) or use of inhaled marijuana within 14 days prior to the Baseline Visit.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):	
Main Exclusion (Continued):	
<p>6. Subject has a history of inflammatory arthritis of different etiology other than axial SpA (including but not limited to rheumatoid arthritis [RA], psoriatic arthritis [PsA], mixed connective tissue disease, systemic lupus erythematosus, reactive arthritis, scleroderma, polymyositis, dermatomyositis, fibromyalgia), or any arthritis with onset prior to 17 years of age.</p> <p>7. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase (AST) > 2 × ULN; serum alanine transaminase (ALT) > 2 × ULN; estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m²; hemoglobin < 10 g/dL; total white blood cell (WBC) count < 2,500/μL; absolute neutrophil count (ANC) < 1,500/μL; absolute lymphocyte count < 800/μL; and platelet count < 100,000/μL.</p>	
Investigational Product:	Upadacitinib
Dose:	15 mg QD
Mode of Administration:	Oral
Reference Therapy:	Placebo
Dose:	N/A
Mode of Administration:	Oral
Duration of Treatment: 104 weeks	
Criteria for Evaluation:	
Efficacy:	
<p>The primary endpoint is the proportion of subjects with ASAS 40 response at Week 14, which is defined as a ≥ 40% improvement and an absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in at least three of the following four domains: patient's global assessment of disease activity (PtGA) (represented by the PtGA 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]), and inflammation (represented by the mean of the two morning stiffness related BASDAI NRS scores [mean of items 5 and 6 of the BASDAI (0 to 10)]), with no worsening at all in the remaining domain.</p> <p>Key multiplicity adjusted secondary efficacy endpoints at Week 14 are:</p> <ol style="list-style-type: none"> 1. Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS); 2. Change from Baseline in MRI Spondyloarthritis Research Consortium of Canada (SPARCC) score (Spine); 3. Proportion of subjects with BASDAI 50 response; 4. Change from Baseline in Ankylosing Spondylitis Quality of Life (AS QoL); 5. Proportion of subjects with ASAS partial remission (PR); 6. Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI); 7. Change from Baseline in Linear Bath Ankylosing Spondylitis Metrology Index (BASMI_{lin}); 8. Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES); 9. Change from Baseline in Work Productivity and Activity Impairment (WPAI); 10. Change from Baseline in ASAS Health Index (HI). 	

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional key secondary efficacy endpoints are:

- Proportion of subjects with ASAS 20 response at Week 14;
- Change from Baseline in MRI SPARCC score (SI joints) at Week 14.

Additional pre-specified endpoints are outlined in the protocol.

Pharmacokinetic:

Blood samples for assay of upadacitinib in plasma will be collected at specified study visits after Baseline. Blood samples at Week 2 and Week 4 visits will be collected prior to dosing, if possible. For all other visits, blood samples will be collected at any time during the visit.

Safety:

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

Statistical Methods:

Efficacy:

All efficacy analyses will be carried out using the Full Analysis Set population, which includes all randomized subjects who receive at least one dose of study drug.

Analysis of the Primary and Key Secondary Endpoints:

Analysis of the primary and key secondary efficacy endpoints will be conducted comparing upadacitinib 15 mg QD versus placebo. The overall type I error rate of the primary and key secondary endpoints will be strongly controlled.

For binary endpoints, frequencies and percentages will be reported for each treatment group.

Comparisons between the upadacitinib group and the placebo group will be conducted using the Cochran-Mantel-Haenszel test, adjusting for main stratification factors.

Analysis of the Primary and Key Secondary Endpoints (Continued):

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Comparisons between the upadacitinib treatment group and the placebo group will be carried out using the Mixed Model for Repeated Measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as fixed effects, and the corresponding baseline values and the main stratification factors as the covariates.

Analysis of Structural Disease Progression:

Progression of structural damage will be assessed using the Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) with conventional radiograph. In addition, evaluation of structural changes in the spine will be explored in subjects who are participating in the low-dose CT scan substudy.

Long-Term Efficacy:

Long-term efficacy by time point will be summarized using descriptive statistics.

Statistical Methods (Continued):

Pharmacokinetic:

Individual plasma concentrations of upadacitinib will be tabulated and summarized. A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values for upadacitinib oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

Safety:

Safety analyses will be carried out using the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug. Safety will be assessed by Treatment Emergent Adverse Events (TEAEs), physical examinations, laboratory assessments, and vital signs. The number and percent of subjects experiencing TEAEs by treatment group will be tabulated by the Medical Dictionary for Drug Regulatory Activities (MedDRA[®]) system organ class (SOC) and preferred terms (PT). In addition, summary of serious adverse events (SAEs) and TEAEs by severity and relationship to study drug as assessed by the Investigators will be provided. SAEs, severe TEAEs, or TEAEs that lead to premature study discontinuation will be listed. The changes in vital signs, physical examination results, and clinical laboratory variables at each visit as compared to baseline will be summarized. Shift of laboratory values from baseline at defined time points will be tabulated.

1.3 List of Abbreviations

ACR	American College of Rheumatology
AD	Atopic Dermatitis
ADL	Activities of Daily Living
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AP	Anteroposterior
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate Transaminase
AUC	Area Under the Curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI _{lin}	Linear Bath Ankylosing Spondylitis Metrology Index
BCG	Bacille Calmette-Guérin
bDMARD	Biologic Disease-Modifying Anti-Rheumatic Drug
BID	Twice Daily (Latin: bis in die)
BUN	Blood Urea Nitrogen
CIA	Collagen-Induced Arthritis
CL/F	Apparent Clearance
C _{max}	Maximum Observed Plasma Concentration
C _{min}	Minimum Observed Plasma Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
csDMARD	Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computer Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events

CXR	Chest X-ray
CYP	Cytochrome P450
DAS	Disease Activity Score
DMARD	Disease-Modifying Anti-Rheumatic Drugs
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient-Reported Outcome
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	Full Analysis Set
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBc Ab	Hepatitis B Core Antibodies
HBs Ab	Hepatitis B Surface Antibodies
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C Virus Antibody
HDL-C	High-density Lipoprotein Cholesterol
HI	Health Index
HIV	Human Immunodeficiency Virus
HIV Ab	Human Immunodeficiency Virus Antibody
HLA-B27	Human Leukocyte Antigen-B27
hsCRP	High Sensitivity C-reactive Protein
IAG	Imaging Acquisition Guideline
IBD	Inflammatory Bowel Disease
ICH	International Council on Harmonization
IEC	Independent Ethics Committee

IGRA	Interferon-Gamma Release Assay
IL-17i	Interleukin-17 Inhibitor
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISI	Insomnia Severity Index
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
JAK	Janus Kinase
LDA	Low Disease Activity
LDL-C	Low-density Lipoprotein Cholesterol
MACE	Major Adverse Cardiovascular Event
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spine Score
MTX	Methotrexate
NCI	National Cancer Institute
NK	Natural Killer
NKT	Natural Killer T
NMSC	Non-Melanoma Skin Cancer
NOAEL	No-Observed-Adverse-Effect-Level
NONMEM	Non-Linear Mixed Effect Modeling
nr-axSpA	non-radiographic Axial Spondyloarthritis
NRI	Non-Responder Imputation
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drug
OC	Observed Cases
PCR	Polymerase Chain Reaction
PD	Premature Discontinuation
PGA	Physician's Global Assessment of Disease Activity
PK	Pharmacokinetic

PPD	Purified Protein Derivative
PR	Partial Remission
PRN	As Needed
PRO	Patient-Reported Outcome
PsA	Psoriatic Arthritis
PT	Preferred Term
PtGA	Patient's Global Assessment of Disease Activity
QD	Once Daily (Latin: quaque die)
QoL	Quality of Life
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Correction Formula
RA	Rheumatoid Arthritis
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RoW	Rest of the World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Sacroiliac
SJC	Swollen Joint Count
SOC	System Organ Class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TJC	Tender Joint Count
TNFi	Tumor Necrosis Factor Alpha Inhibitor
ULN	Upper Limit of Normal
UC	Ulcerative Colitis
US	United States
V/F	Apparent Volume of Distribution
VHP	Voluntary Harmonization Procedure
WBC	White Blood Cell

WPAI

Work Productivity and Activity Impairment

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3.0 Introduction

Ankylosing Spondylitis

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 (IBD) related arthritis, and undifferentiated SpA.¹ A more universally consistent way of categorizing SpA patients would be to define them by their primary and predominant clinical manifestation of axial or peripheral SpA.²

Axial SpA encompasses a spectrum of disease manifestations, which has been split into two categories, AS and non-radiographic axial SpA (nr-axSpA), due to the 1984 modified New York criteria, which require the presence of sacroiliitis on plain conventional radiographs for the classification of AS.³ Clinically, patients with AS and nr-axSpA have comparable clinical manifestations and burden of disease, with the sole differentiating characteristic between the two categories of axial SpA being the presence of sacroiliitis visualized by plain radiographs for the classification of AS.^{4,5}

The Assessment of SpondyloArthritis international Society (ASAS) has proposed and validated new classification criteria for patients with axial SpA⁶ and for those with peripheral SpA.²

The prevalence of AS differs between regions and has been estimated to be up to 0.5%⁷⁻⁹ with similar estimated prevalence rates for nr-axSpA, resulting in an overall prevalence for axial SpA in the United States of approximately up to 1% or even higher in the overall population.^{10,11}

Recently, the ASAS and European League Against Rheumatism (EULAR) have published updated treatment recommendations for the whole group of axial SpA.¹² The first-line treatment of axial SpA consists of NSAIDs. After the failure of one NSAID, a change to a second NSAID is recommended. In patients with persistently high disease activity despite a course of two NSAIDs given over a total of at least 4 weeks, initiation of

a biologic disease-modifying anti-rheumatic drug (bDMARD) is recommended, and current practice is to start with a tumor necrosis factor alpha inhibitor (TNFi). If TNFi therapy fails, switching to another TNFi or an interleukin 17 inhibitor (IL-17i) is recommended. This recommendation is based on randomized controlled AS studies with TNFi and the IL-17i secukinumab that showed an overall good benefit-risk profile.¹³⁻²⁰ Several TNFi have also been successfully evaluated in nr-axSpA in controlled studies.^{17,21-23} Despite recent advances in the treatment of axial SpA, there remains a significant unmet medical need as only approximately 45% to 50% of patients show an ASAS 40 response and only approximately 15% to 20% achieve a state of remission. In addition, treatment options are still limited when compared with other rheumatic diseases such as rheumatoid arthritis (RA) or PsA. In axial SpA, csDMARDs and long-term corticosteroids are not efficacious and therefore not recommended for treatment of axial symptoms.¹²

Other than TNFi and secukinumab, ustekinumab, an IL-12/23 inhibitor, has shown efficacy in axial SpA in a small open-label Phase 2 trial.²⁴ Also, recently, the JAK inhibitor tofacitinib has demonstrated efficacy in a placebo-controlled Phase 2 AS study, showing efficacy on signs and symptoms, as well as reduction of active inflammation both in the spine and sacroiliac (SI) joints on MRI.²⁵

Overview of Upadacitinib (ABT-494)

Inhibition of JAK-mediated pathways is a promising approach for the treatment of patients with chronic inflammatory diseases such as axial SpA. AbbVie is developing a small molecule inhibitor of JAK, upadacitinib, that may address the current needs.

The JAK family is composed of 4 family members: JAK1, 2, 3, and Tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors such as common gamma-chain receptors and the glycoprotein 130 transmembrane proteins.²⁶ Activation of JAK pathways initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular

trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders.

Hence, the JAK family has evoked considerable interest in the area of inflammatory diseases, leading to the development of various JAK inhibitors with different selectivity profiles against JAK1, JAK2, JAK3, and Tyk2. Tofacitinib, the first in this class, has been approved in the United States, Europe, and in other countries for treating moderately to severely active RA patients. Although tofacitinib, a non-selective JAK inhibitor, improves the clinical signs and symptoms and inhibits structural progression in RA patients, questions regarding the safety profile remain, including serious infections, herpes zoster reactivation, malignancies, and hematologic adverse events (AEs).

The second generation of JAK inhibitors, with different selectivity profiles against JAK1, JAK2, JAK3, and Tyk2, are in development. Upadacitinib is a novel JAK1 inhibitor being developed for the treatment of adult patients with inflammatory diseases (RA, Crohn's disease [CD], ulcerative colitis [UC], atopic dermatitis [AD], and PsA). Based on in vitro selectivity assays and in vivo animal models, upadacitinib has demonstrated inhibition of JAK1 at efficacious drug exposure levels. The enhanced selectivity of upadacitinib may have the potential for an improved benefit/risk profile by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis. Upadacitinib is also less potent against JAK3, an important component of lymphocyte activation and function. As such, treatment with upadacitinib, a selective JAK1 inhibitor with reduced JAK3 inhibition, could result in a decreased risk for infection (including viral reactivation) and/or malignancy compared to less selective JAK inhibitors.

Additional information regarding indications under study can be found in the current Investigator's Brochure.²⁷

3.1 Differences Statement

Study M16-098 differs from other upadacitinib studies as it is the first study to evaluate the safety and efficacy of upadacitinib in subjects with AS.

3.2 Benefits and Risks

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.²⁷ The results of all genetic toxicology testing indicate that upadacitinib is not genotoxic. Embryonic and fetal development studies indicate that upadacitinib is teratogenic in both rats and rabbits. Based on these findings, all women of childbearing potential must agree to use protocol-specified pregnancy avoidance measures as outlined in the protocol.

To date, upadacitinib has been studied in two Phase 2 studies in subjects with RA and is being evaluated in CD, UC, AD, and PsA. Two Phase 2 studies have been completed: two randomized controlled trials (Study M13-550 [NCT01960855] and Study M13-537 [NCT02066389]) in 575 subjects with moderately to severely active RA on background methotrexate (MTX). Four Phase 2 studies are ongoing: one open-label extension to the completed RA studies (Study M13-538 [NCT02049138]); one randomized, dose-ranging, placebo-controlled study in subjects with moderately to severely active CD (Study M13-740 [NCT02365649]); one randomized, double-blind, placebo-controlled study in subjects with moderately to severely active UC (Study M14-234 [NCT02819635]); and one randomized, dose-ranging, placebo-controlled study in subjects with moderate to severe AD (Study M16-048 [NCT02925117]). The Phase 3 clinical development programs for RA and PsA have been initiated, and enrollment in the RA studies is ongoing.

Results are available from two RA Phase 3 clinical trials (Study M13-549 [NCT02675426] and Study M13-542 [NCT02706847]) evaluating upadacitinib 15 mg QD and 30 mg QD in subjects with moderate to severe RA. Study M13-549 evaluated upadacitinib compared to placebo in subjects with inadequate response to csDMARDs. At Week 12, among subjects receiving upadacitinib 15 mg (n = 221) or 30 mg QD (n = 219), 64% and 66% achieved ACR20, respectively, compared to 36% of subjects receiving placebo (n = 221) ($P < 0.001$). Similarly, the rate of subjects achieving ACR50 and ACR70 was also significantly higher in the upadacitinib groups – ACR50 of 38%,

43%, and 15% and ACR70 of 21%, 27%, and 6% in the upadacitinib 15 mg, 30 mg, and placebo groups, respectively ($P < 0.001$ for all comparisons). Low disease activity (LDA), based on a DAS28 (CRP) of ≤ 3.2 , was achieved by 48% of subjects receiving either dose of upadacitinib, compared to 17% of subjects receiving placebo ($P < 0.001$).²⁸

Study M13-542 evaluated upadacitinib compared to placebo in subjects with inadequate response to bDMARDs. At Week 12, among subjects receiving upadacitinib 15 mg ($n = 164$) or 30 mg QD ($n = 165$), 65% and 56% of subjects receiving upadacitinib 15 mg or 30 mg QD achieved ACR20, respectively, compared to 28% of subjects receiving placebo ($n = 169$) ($P < 0.001$). Similarly, the rate of subjects achieving ACR50 and ACR70 was also higher in the upadacitinib groups – ACR50 of 34%, 36%, and 12% and ACR70 of 12%, 23%, and 7% in the upadacitinib 15 mg, 30 mg, and placebo groups, respectively ($P < 0.001$ for all comparisons except ACR70 for the 15 mg dose). Low disease activity, based on a DAS28 (CRP) of ≤ 3.2 , was achieved by 43% and 42% of subjects receiving upadacitinib 15mg and 30 mg, respectively, compared to 14% of subjects receiving placebo ($P < 0.001$).²⁹

Data on the safety of treatment with upadacitinib are available from the Phase 2 studies in patients with RA.^{30,31} Safety data from these two Phase 2 studies ($N = 575$) showed that the types and frequencies of AEs during upadacitinib treatment were consistent with subjects with moderately to severely active RA receiving immunomodulatory therapy. The incidences of AEs were numerically higher in the upadacitinib dose groups, with a trend toward higher rates with higher doses of upadacitinib. The most frequently reported AEs ($\geq 5\%$) in the upadacitinib-treated subjects were urinary tract infection, headache, upper respiratory tract infection, and nausea. There were 6 subjects (1.3% of total combined populations) with herpes zoster reactivation distributed across the upadacitinib dose groups, and 2 subjects (1.9%) in the placebo groups. In these two 12-week studies, a total of 2 subjects in the upadacitinib treatment groups reported malignancies. One subject reported non-melanoma skin cancers (NMSC) (basal cell and squamous cell carcinoma), and 1 subject was diagnosed with lung cancer 11 days after the final scheduled visit and subsequently died 14 weeks after study completion. These events

were reported by the Investigators as not possibly related to study drug. No events of gastrointestinal perforation were reported. Elevations of liver function tests were sporadic with no clear dose-response relationship observed.

As observed with other JAK inhibitors, treatment with upadacitinib resulted in an increase in lipids (low-density lipoprotein cholesterol [LDL-C] and high density lipoprotein cholesterol [HDL-C]). There was a trend for lower red blood cell counts, especially at the two highest doses (12 mg twice daily [BID] and 18 mg BID); lower white blood cell counts; and reductions in Natural Killer (NK) cells. Among subjects with laboratory evidence of systemic inflammation (as evidenced by hsCRP > upper limit of normal [ULN]), treatment with lower doses of upadacitinib (3 mg BID and 6 mg BID) was associated with improvements in mean hemoglobin relative to placebo. At higher doses, there was a reduction in mean hemoglobin; however, the mean hemoglobin levels remained within normal range throughout the treatment period. In the two Phase 3 studies in RA (Studies M13-549 and M13-542), the safety profile was consistent with that observed in the upadacitinib Phase 2 clinical trials in RA. Events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib.

No studies in subjects with axial SpA have been performed with upadacitinib. The ability of upadacitinib to modulate inflammation and bone formation in vivo was assessed using collagen-induced arthritis (CIA) in rats. The extended rat CIA preclinical model is supportive of inflammation-driven new bone formation in SpA. Oral doses of upadacitinib at 1, 3 and 10 mg/kg BID for 4 weeks, starting at peak inflammation in the model, resulted in a dose-dependent inhibition of inflammation, as well as bone destruction and new bone formation based on paw swelling scores, microCT evaluation of bone, and histologic evaluation of the arthritic paw. At the study endpoint, there was both significant joint destruction and periosteal bone formation in the arthritic ankle in vehicle-treated animals. Upadacitinib inhibition of new bone formation in an extended rat CIA model provides supportive data for further evaluation of upadacitinib in axial SpA.

In summary, upadacitinib is a novel selective JAK1 inhibitor with the ability to decrease joint inflammation and damage mediated by JAK signaling. The Phase 2 program with upadacitinib in RA demonstrated efficacy for improvement in signs and symptoms of RA, and the safety results were consistent with those known to be associated with JAK inhibition.³⁰⁻⁴⁰ Current clinical data have not identified any new safety issues of concern compared to what is known about JAK inhibition in immune-mediated inflammatory diseases. Upadacitinib is currently being tested in Phase 3 in RA. Also, the Phase 2 study with tofacitinib established proof of mechanism of JAK inhibition in AS.²⁵

Taken together, the data from a preclinical extended rat CIA model, the safety and efficacy data from the Phase 2 RA program and two Phase 3 studies in RA, as well as the data from the tofacitinib Phase 2 AS study, support the investigation of upadacitinib 15 mg QD in subjects with AS. A detailed rationale on the selection of the dose is provided in Section 5.6.4. The current Phase 2/3 Study M16-098 will assess the benefit-to-risk profile of upadacitinib in subjects with active AS who have had an inadequate response to at least two NSAIDs or intolerance to or a contraindication for NSAIDs, and who are bDMARD-naïve.

4.0 Study Objective

The primary objectives of the study are:

Period 1

1. To evaluate the efficacy of upadacitinib compared with placebo on reduction of signs and symptoms as measured by the proportion of subjects who achieve an ASAS 40 response at Week 14 in subjects with active AS who have had an inadequate response to at least two NSAIDs or intolerance to or a contraindication for NSAIDs, and who are bDMARD-naïve.
2. To assess the safety and tolerability of upadacitinib in subjects with active AS who have had an inadequate response to at least two NSAIDs or intolerance to or a contraindication for NSAIDs, and who are bDMARD-naïve.

Period 2

To evaluate the safety, tolerability, and efficacy of upadacitinib through up to 2 years of treatment in subjects who have completed Period 1.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2/3 multicenter study that includes two periods. Period 1 is a 14-week randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo for the treatment of subjects with active AS who have had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or intolerance to or a contraindication for NSAIDs as defined by the Investigator, and who are bDMARD-naïve.

Period 2 is an open-label long-term extension to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with AS who have completed Period 1.

The study was designed to enroll approximately 170 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

The study duration will include a 35-day screening period; a 14-week randomized, double-blind, placebo-controlled period (Period 1); a 90-week open-label extension period (Period 2); and a 30-day follow-up visit.

X-ray of the pelvis will be performed within the 35-day screening period to evaluate the SI joints to confirm the fulfillment of the modified New York Criteria for AS ([Appendix C](#)). X-ray of the spine will also be performed within the 35-day screening period to assess for total spinal ankylosis; subjects with total spinal ankylosis are not eligible for this study. The x-rays of the spine and pelvis will not be required during the

Screening Period if the subject had a previous anteroposterior (AP) pelvis x-ray and lateral spine x-rays within 90 days of the Screening Period, provided that the x-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to one of two treatment groups:

- Group 1: Upadacitinib 15 mg QD (n = 85)
- Group 2: Placebo (n = 85)

Randomization will be stratified by Screening hsCRP (\leq ULN vs. $>$ ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

If entering the study on concomitant csDMARDs (i.e., MTX, leflunomide, sulfasalazine [SSZ], and/or hydroxychloroquine), the subject must be on a stable dose for ≥ 4 weeks prior to the first dose of study drug. If entering the study on concomitant oral corticosteroids, subject must be on a stable dose of prednisone (≤ 10 mg/day) or oral corticosteroid equivalents for at least 14 days prior to the first dose of study drug. The dose(s) of csDMARDs and corticosteroids should remain stable throughout the study (except as described for rescue therapy), but may be decreased only for safety reasons.

If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen and codeine or hydrocodone, and/or non-opioid analgesics, subject must be on stable dose(s) for at least 14 days prior to the first dose of study drug and should remain stable throughout the study (except as described for rescue therapy), but may be decreased only for safety reasons.

Starting at Week 16, subjects who do not achieve at least an ASAS 20 response at two consecutive visits will have the option to add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of

acetaminophen and codeine or hydrocodone), and/or modify dose of MTX or SSZ at Week 20 or thereafter.

Starting at Week 24, subjects who still do not achieve at least an ASAS 20 response at two consecutive visits will be discontinued from study drug treatment.

Subjects who complete the Week 14 visit (end of Period 1) will enter the open-label long-term extension portion of the study, Period 2 (90 weeks). Subjects who are assigned to upadacitinib in Period 1 will continue to receive upadacitinib 15 mg QD in an open-label manner. Subjects who were randomized to placebo at Baseline will also receive open-label upadacitinib 15 mg QD at Week 14.

The primary analysis will be conducted after all subjects have completed Week 14 or have prematurely discontinued prior to Week 14. Study sites and subjects will remain blinded for the duration of the study (Periods 1 and 2).

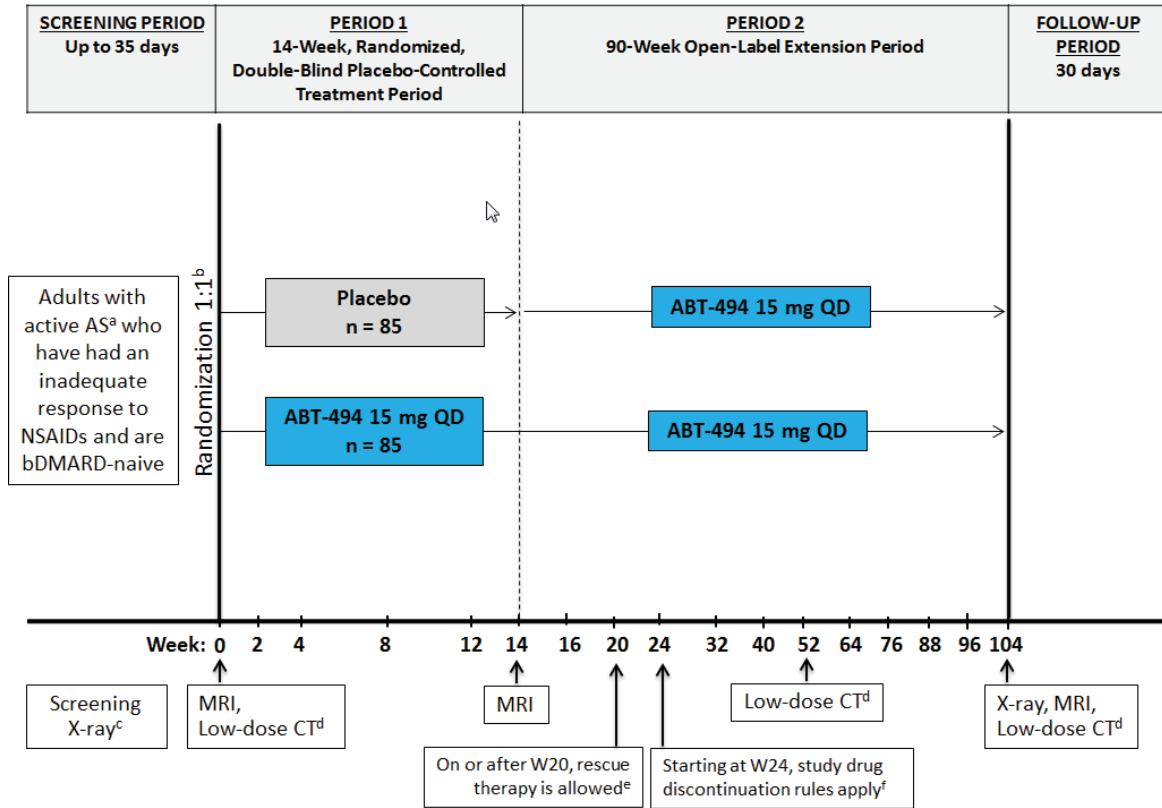
Optional samples may be collected for exploratory research at designated time points throughout the study.

Subjects will have an x-ray of the spine at Week 104. All subjects who meet eligibility criteria will have an MRI evaluation of the SI joints, as well as the cervical, thoracic, and lumbar regions of the spine, prior to or at the Baseline Visit, at Week 14, and Week 104.

Subjects at select sites who consent to participate in the low-dose CT scan substudy and meet eligibility criteria will have low-dose CT scan evaluation of the whole spine (cervical, thoracic, and lumbar spine) prior to or at the Baseline Visit, Week 52, and Week 104.

Study design schematic is shown in [Figure 1](#).

Figure 1. Study Design



AS = ankylosing spondylitis; ASAS = Assessment of SpondyloArthritis international Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; bDMARD = biologic disease-modifying antirheumatic drugs; CT = computer tomography; hsCRP = high sensitivity C-reactive protein; MRI = magnetic resonance imaging; NRS = numeric rating scale; NSAIDs = nonsteroidal anti-inflammatory drugs; QD = once daily; RoW = Rest of the World; SSZ = Sulfasalazine; ULN = upper limit of normal; W = week

- Clinical diagnosis of AS and meeting the modified New York Criteria for AS. Subject must have baseline disease activity as defined by having BASDAI score ≥ 4 and Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 NRS at the Screening and Baseline Visit.
- Stratified by geographic region (US/Canada, Japan, RoW) and hsCRP (\leq ULN vs. $>$ ULN).
- The x-rays of the spine and pelvis will not be required during the Screening Period if the subject had a previous anteroposterior pelvis x-ray and lateral spine x-rays within 90 days of the Screening Period, provided that the x-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.
- For subjects at select sites who consent to participation in the low-dose CT scan substudy.

Figure 1. Study Design (Continued)

- e. Starting at Week 16, subjects who do not achieve at least an ASAS 20 response at two consecutive visits will have the option to add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or modify dose of MTX or SSZ at Week 20 or thereafter.
- f. Starting at Week 24, subjects who still do not achieve at least an ASAS 20 response at two consecutive visits will be discontinued from study drug treatment.

Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures and then provide a signed and dated informed consent before undergoing the screening procedures outlined in Section 5.3.1.1. Lab values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if initial samples were unable to be analyzed would not count as a retest since an initial result was never obtained.

Subjects that initially screen fail for the study are permitted to re-screen once following re-consent. Lab values can be re-tested once during the re-screening period. For additional re-screening, AbbVie Therapeutic Area Medical Director (TA MD) approval is required. All screening procedures with the possible exceptions noted below will be repeated during re-screening. The subject must meet all the 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.

If the subject had a complete initial screening evaluation, including the following assessments, these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met, there are no changes in the subject's medical history that would warrant re-testing, and no more than 90 days have passed:

- Hepatitis B virus (HBV), Hepatitis C virus (HCV), and human immunodeficiency virus (HIV) serology

- Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test or equivalent) and/or a purified protein derivative (PPD) test (or both if required per local guidelines)
- Chest x-ray (CXR)
- Electrocardiogram (ECG)

The x-rays of the spine and pelvis will not be required during the Screening Period if the subject had a previous AP pelvis x-ray and lateral spine x-rays within 90 days of the Screening Period, provided that the x-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.

Period 1 (14-Week Randomized, Double-Blind, Placebo-Controlled Treatment Period)

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 14 Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the study and randomized to double-blind treatment. During this period of the study, subjects will visit the study site at Weeks 2, 4, 8, 12, and 14. A ± 3 day window is permitted around scheduled study visits. The last dose of oral study drug in Period 1 is taken the day prior to the Week 14 visit.

Period 2 (90-Week Open-Label Extension Period)

Period 2 will begin at the Week 14 visit after all assessments have been completed. At Week 14, subjects on placebo will receive open-label upadacitinib 15 mg QD. Subjects on upadacitinib 15 mg QD will continue to receive the same treatment in an open-label manner. During Period 2, subjects will have a study visit at Weeks 16, 20, 24, 32, 40, 52, 64, 76, 88, 96, and 104. A ± 7 day window is permitted around scheduled study visits. Starting at Week 24, subjects who do not achieve at least an ASAS 20 response compared with Baseline at two consecutive visits will be discontinued from study drug treatment (see Section 5.4.1).

Discontinuation of Study Drug and Continuation of Study Participation

Subjects may discontinue study drug treatment, but may choose to continue to participate in the study (refer to Section 5.4.1 for additional details). Subjects who prematurely discontinue study drug should complete a Premature Discontinuation (PD) Visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule and adhere to all study procedures except for dispensing study drug, pharmacokinetic (PK) sample collection, and blood sample collection for optional exploratory research and validation studies. In addition, future ASAS 20 nonresponse discontinuation criteria no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time (refer to Section 5.4.1 for additional details). If a subject prematurely discontinues study drug treatment AND study participation (withdrawal of consent), the procedures outlined for the PD Visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, a 30-day follow-up visit (or phone call if a visit is not possible) should occur to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs.

Follow-Up Period

A Follow-Up Visit (or phone call if a visit is not possible) will occur approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AE/SAEs and to collect vital signs and clinical laboratory tests.

Subjects will complete the Follow-Up Visit when they have either:

- Completed the last visit of the study; OR

- Prematurely discontinued study drug and/or study participation and have completed a PD visit. In this case the 30 day Follow-Up Visit may be a telephone call if a site visit is not possible. Vital signs and laboratory tests may not be required. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least one study visit at least 30 days after last dose of study drug.

5.2 Selection of Study Population

It is anticipated that approximately 170 subjects with AS will be randomized at approximately 107 study centers, globally.

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. Male or female \geq 18 years of age.
2. Subject with a clinical diagnosis of AS and meeting the modified New York Criteria for AS ([Appendix C](#)).²
3. Subject must have baseline disease activity as defined by having a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score \geq 4 and a Patient's Assessment of Total Back Pain score \geq 4 based on a 0 – 10 Numeric Rating Scale (NRS) at the Screening and Baseline Visits.
4. Subject has had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses, or subject has an intolerance to or contraindication for NSAIDs as defined by the Investigator.
5. Women of childbearing potential (refer to Section 5.2.4), must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing. Note: subjects with

borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

6. If female, subject must be postmenopausal, OR permanently surgically sterile, OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
 - Additional local requirements may apply. Refer to [Appendix D](#) for local requirements.
7. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of oral study drug, to practice the protocol-specified contraception (refer to Section 5.2.4).
 - Additional local requirements may apply. Refer to [Appendix D](#) for local requirements.
8. If entering the study on concomitant MTX, leflunomide, SSZ, and/or hydroxychloroquine, subject must be on a stable dose of MTX (≤ 25 mg/week) and/or SSZ (≤ 3 g/day) and/or hydroxychloroquine (≤ 400 mg/day) or leflunomide (≤ 20 mg/day) for at least 28 days prior to the Baseline Visit. A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
9. If entering the study on concomitant oral corticosteroids, subject must be on a stable dose of prednisone (≤ 10 mg/day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline Visit.
10. If entering the study on concomitant NSAIDs, tramadol, combination of acetaminophen and codeine or hydrocodone, and/or non-opioid analgesics, subject must be on stable dose(s) for at least 14 days prior to the Baseline Visit.

11. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, CXR, and a 12-lead ECG performed at the Screening Visit.
12. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. For subjects in Japan only: In case of subjects under 20 years of age, the subjects and their parents or legal guardians must voluntarily sign and date an informed consent.

Rationale for the Inclusion Criteria

Inclusion Criteria	Rationale
1 – 4, 8 – 11	To select the appropriate subject population for this study
5 – 7	The effect of upadacitinib on pregnancy and reproduction is unknown
12	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Prior exposure to any biologic therapy with a potential therapeutic impact on SpA (refer to Section 5.2.3.3 for examples of prohibited biologic therapy).
3. Subject has been treated with any investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.

4. Intra-articular joint injections, spinal/paraspinal injection(s), or parenteral administration of corticosteroids within 28 days prior to the Baseline Visit. Inhaled or topical corticosteroids are allowed.
5. Subject on any other DMARDs (other than those allowed), thalidomide, or apremilast within 28 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit.
6. Subject on opioid analgesics (except for combination acetaminophen/codeine or acetaminophen/hydrocodone which are allowed) or use of inhaled marijuana within 14 days prior to the Baseline Visit.
7. Subject has a history of inflammatory arthritis of different etiology other than axial SpA (including but not limited to RA, PsA, mixed connective tissue disease, systemic lupus erythematosus, reactive arthritis, scleroderma, polymyositis, dermatomyositis, fibromyalgia), or any arthritis with onset prior to 17 years of age.
8. Subject with extra-articular manifestations (e.g., psoriasis, uveitis, or IBD) that are not clinically stable for at least 30 days prior to study entry.
9. Subject has total spinal ankylosis.
10. Subject has undergone spinal or joint surgery at joints to be assessed within this study within 60 days prior to the Baseline Visit 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.
11. Subject is permanently wheelchair-bound or bedridden.
12. Receipt of any live vaccine within 4 weeks (8 weeks in Japan) prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks (8 weeks in Japan) after the last dose of study drug.
13. Systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to [Table 1](#) for examples of commonly used strong CYP3A inhibitors and inducers).

14. Use of oral traditional Chinese medicine within 4 weeks prior to the Baseline visit.
15. Any active, chronic or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or human immunodeficiency virus (HIV). HBV, HCV, and HIV infections are defined as:
 - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for Hepatitis B core antibody (HBc Ab) positive (+) subjects (and for Hepatitis B surface antibody (HBs Ab) positive [+] subjects in Japan only);
 - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
 - HIV: confirmed positive anti-HIV antibody (HIV Ab) test.
16. Subject has active TB or meets TB exclusionary parameters (refer to Section 5.3.1.1 for specific requirements for TB testing).
17. Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior the first dose of study drug.
18. History of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix.
19. History of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for gastrointestinal perforation per Investigator judgment.
20. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome.
21. Subject has been a previous recipient of an organ transplant.

22. History of recent (within past 6 months) cerebrovascular accident, myocardial infarction, or coronary stenting.
23. History of any condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.
24. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
25. History of an allergic reaction or significant sensitivity to constituents of the study drug(s) (and their excipients) and/or other products in the same class.
26. Subject has contraindication to MRI or any condition that would interfere with the ability to perform an MRI.
27. Female subject who is breastfeeding or considering becoming pregnant during the study.
28. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:
 - Serum aspartate transaminase (AST) $> 2 \times$ ULN;
 - Serum alanine transaminase (ALT) $> 2 \times$ ULN;
 - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m²;
 - Hemoglobin < 10 g/dL;
 - Total white blood cell count (WBC) $< 2,500/\mu\text{L}$;
 - Absolute neutrophil count (ANC) $< 1,500/\mu\text{L}$;
 - Absolute lymphocyte count $< 800/\mu\text{L}$;
 - Platelet count $< 100,000/\mu\text{L}$.
29. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
30. For Japan subjects only: positive result of beta-D-glucan.

Rationale for the Exclusion Criteria

Exclusion Criteria	Rationale
1 – 2, 9 – 11	To select the appropriate subject population in the study
3 – 8, 12 – 26, 28 – 30	To ensure safety of the subjects throughout the study
27	The impact of upadacitinib on pregnancies is unknown

5.2.3 Prior, Concomitant, and Prohibited Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving within 28 days prior to Screening, 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. Also, medications including but not limited to DMARDs taken for AS since date of AS diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior Therapy

All prior drug therapies for AS since initial diagnosis must be recorded in the eCRF, along with the dates of first and last dose, maximum dosage taken, route of administration, and reason for discontinuation, if known. Additionally, the Investigator will record history of response to NSAIDs (e.g., no response, inadequate response, loss of response), intolerance to NSAIDs, and/or contraindication for NSAIDs.

5.2.3.2 Permitted Background AS Therapy

Subjects should continue on their stable (≥ 4 weeks prior to the first dose of study drug) background csDMARD therapy (restricted to oral or parenteral MTX [≤ 25 mg per week], SSZ [≤ 3 g/day], hydroxychloroquine [≤ 400 mg/day], and leflunomide [≤ 20 mg/day])

throughout the study. A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide. At any time, the csDMARD dose may be decreased only for safety reasons. Subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent such as folinic acid) throughout study participation. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions. AbbVie will not provide the csDMARDs (or folic acid, if taking MTX).

Subjects should also continue on their stable doses of NSAIDs, tramadol, combination acetaminophen/codeine, acetaminophen/hydrocodone, and/or non-opioid analgesics; oral corticosteroids (equivalent to prednisone ≤ 10 mg/day); or inhaled corticosteroids. At any time, the dose of NSAIDs, tramadol, combination acetaminophen/codeine, acetaminophen/hydrocodone, and/or non-opioid analgesics, or oral corticosteroids may be decreased only for safety reasons.

- If taking any of the above on a scheduled basis, they should continue to take them as they did at study entry with no change in dose or frequency, including on study visit days.
- If not taking any of the above at Baseline, these must not be initiated except where permitted by protocol.
- If taking any of the above at Baseline on an as-needed basis (PRN), they should continue to use them for the same reason and same dose each time but they should not be taken within the 24 hours prior to any study visit to avoid bias in outcome measurements.

For subjects on concomitant NSAID therapy, the NSAID eCRF should be completed.⁴¹

One intra-articular corticosteroid injection for a peripheral joint will be allowed during Period 1 of the study. In Period 2, intra-articular corticosteroid injections for peripheral joints are allowed at the Investigator's discretion. Once a joint is injected, it will be considered not evaluable/assessable ("NA") during the 90 days following injection. PRN use of inhaled corticosteroids is permitted at any time.

In the event of tolerability (or other safety) issues, the doses of these medications may be decreased or discontinued.

Rescue Therapy

Starting at Week 16, subjects who do not achieve at least an ASAS 20 response at two consecutive visits will have the option to add or modify doses of NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or modify dose of MTX or SSZ at Week 20 or thereafter (after assessments have been performed). Change in dose or addition of DMARDs other than MTX or SSZ is not permitted for rescue.

Starting at Week 24, subjects who still do not achieve at least an ASAS 20 response at two consecutive visits will be discontinued from study drug treatment.

5.2.3.3 Prohibited Therapy

JAK Inhibitor

Prior exposure to JAK inhibitors (including but not limited to tofacitinib [Xeljanz[®]], baricitinib, and filgotinib) is not allowed.

Corticosteroids

Spinal/paraspinal and SI joint injection(s) or parenteral administration of corticosteroids are not allowed, and subjects must have discontinued use at least 28 days prior to the first dose of study drug.

Inhaled or topical corticosteroids are allowed.

Biologic Therapies

All biologic therapies with a potential therapeutic impact on SpA are prohibited during the study (i.e., Periods 1 and 2).

Subjects with prior exposure to bDMARDs are excluded from participation in this study.

Examples of biologic therapies include but are not limited to the following:

- Humira[®] (adalimumab)
- Enbrel[®] (etanercept)
- Remicade[®] (infliximab)
- Simponi[®] (golimumab)
- Cimzia[®] (certolizumab pegol)
- Cosentyx[®] (secukinumab)
- Taltz[®] (ixekizumab)
- Stelara[®] (ustekinumab)
- Orencia[®] (abatacept)
- Kineret[®] (anakinra)
- Rituxan[®] (rituximab)
- Actemra[®] (tocilizumab)
- Raptiva[®] (efalizumab)
- Tysabri[®] (natalizumab)
- Benlysta[®] (belimumab)

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study (i.e., end of Period 2). The most common strong CYP3A inhibitors and inducers are listed in [Table 1](#).

Table 1. Examples of Commonly Used Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Voriconazole	Avasimibe Carbamazepine Phenytoin Rifampin St. John's Wort

Opiates and Marijuana

High potency opiates or use of inhaled marijuana are not permitted during the study (i.e., Periods 1 and 2), and subjects must have discontinued use at least 14 days prior to the first dose of study drug. High-potency opiates include but are not limited to:

- oxycodone
- oxymorphone
- fentanyl
- levorphanol
- buprenorphine
- methadone
- hydromorphone
- morphine
- meperidine

Combination of acetaminophen and codeine or hydrocodone is allowed.

Investigational Drugs

Subjects who have been treated with any investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in this study. Investigational drugs are also prohibited during the study.

Vaccines

Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. If the subject and Investigator choose to administer live vaccines, these vaccinations must be completed (per local label) at least 4 weeks (8 weeks in Japan) before first dose of study drug with appropriate precautions. Live vaccines are prohibited during the study. Examples of live vaccines include but are not limited to the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Herpes zoster;
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid.

Examples of common vaccines that are inactivated, toxoid, or biosynthetic include but are not limited to: injectable influenza vaccine, pneumococcal, and pertussis (Tdap) vaccines.

Traditional Chinese Medicine

Oral traditional Chinese medicine is not permitted during the study, and subjects must have discontinued traditional Chinese medicine at least 4 weeks prior to the first dose of study drug.

5.2.4 Contraception Recommendations

Contraception Recommendation for Females

A woman who is postmenopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Postmenopausal is defined as:

- Age \geq 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age $<$ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle stimulating hormone (FSH) level $>$ 40 mIU/mL.

If the female subject is $<$ 55 years of age AND has had no menses for \geq 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.

- If FSH is not tested, it is assumed that the subject is of childbearing potential, and protocol-specified contraception is required.
- If the FSH is tested and the result is consistent with post-menopausal status, contraception is not required.
- If the FSH is tested and the result is consistent with pre-menopausal status, contraception is required, and a serum pregnancy test must be performed (see Section 5.3.1.1, Pregnancy Test).

For a female subject at any age:

- Female subjects with menses within the past 12 months are of childbearing potential, and FSH is therefore not required, but contraception is required.
- Female subjects who are surgically sterile (defined above) are not of childbearing potential, and therefore, no FSH testing or contraception is required.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly-effective methods of birth control that is effective from Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Bilateral tubal occlusion/ligation (Japan only: bilateral tubal ligation only).
- Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable.)

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the highly effective birth control methods listed above (excluding true abstinence).

If during the course of the study a woman becomes surgically sterile or post-menopausal (defined above) and complete documentation is available, contraceptive measures as defined above are no longer required.

It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib. Contraception requirements of the allowed background medications should be carefully followed during use and after discontinuation of these drugs and should be based on the local label.

Additional local requirements may apply. Refer to [Appendix D](#) for local requirements for Canada and Korea.

Contraception Recommendation for Males

For a male subject who has a female partner who is postmenopausal or permanently sterile, no contraception is required.

A male subject who is sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 30 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the contraceptive measures as defined in the protocol for female study subjects of childbearing potential.
- OR
- True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable.)

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 30 days after the last dose of study drug.

Male subjects are responsible for informing his partner(s) of the risk of becoming pregnant and for reporting any pregnancy to the study doctor. If a pregnancy occurs, a partner authorization form requesting pregnancy outcome information will be requested from the pregnant partner.

It is important to note that contraception and sperm donation recommendations described above are specifically intended to prevent pregnancy during and after exposure to the investigational therapy upadacitinib. Contraception requirements of the background medications should be carefully followed during use and after discontinuation of these drugs and should be based on the local label.

Additional local requirements may apply. Refer to [Appendix D](#) for local requirements for Canada and Korea.

5.3 Efficacy, Pharmacokinetic, Exploratory Research and Validation Studies, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Subjects will be allowed a visit window of ± 3 days for all study visits (with the exception of the Baseline Visit, as the screening window is a maximum of 35 days) up to the Week 14 visit. Visits after the Week 14 visit will have a visit window of ± 7 days.

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 described are listed in the following section of this protocol and are summarized in tabular format in [Appendix E](#).

5.3.1.1 Study Procedures

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in [Appendix E](#), with the exception of exploratory research and validation studies (discussed in Section [5.3.1.2](#) and summarized in tabular format in

[Appendix F](#)), drug concentration measurements (discussed in Section 5.3.2), the collection of prior and concomitant medication information (discussed in Section 5.2.3), and the collection of AE information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

At the Screening visit, the subject will sign and date a study-specific, IEC/IRB-approved informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Separate written consent will be required for each subject in order to participate in the optional exploratory research and validation studies. Details regarding how informed consent will be obtained and documented are provided in Section 9.3. Subjects can withdraw informed consent at any time.

Inclusion/Exclusion Criteria

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

Medical and Surgical History

A complete non-AS-related medical and surgical history, including history of alcohol and nicotine use, will be taken from each subject during the Screening Visit. Additionally, a list of each subject's specific AS-related medical and surgical history will be recorded at Screening. History of herpes zoster, herpes zoster vaccination, and hepatitis B vaccination status will be recorded as part of the medical history. An updated medical history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment.

A detailed medical history with respect to TB risk factors will be documented in the study source documentation. This information will include BCG vaccination; cohabitation with individuals who have had TB; and travel to, residence in, or work in TB endemic locations.

Vital Signs, Height, and Weight

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at visits specified in [Appendix E](#). Vital signs should be performed before blood draws are performed. Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits as specified in [Appendix E](#). All measurements will be recorded in metric units where applicable.

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), and treatment received for at least one episode since the last visit.⁴² 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 subject self-reported.

Psoriasis

At Baseline and all subsequent visits, the Investigator will document prior or new diagnosis of psoriasis, including the current status.⁴² The corresponding eCRF should be completed. The subject's right or left hand should be selected as the measuring device to estimate the area of involvement. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1%.

Inflammatory Bowel Disease

At Baseline and all subsequent visits, the Investigator will document prior or new diagnosis of IBD and the specific treatment since the last visit.⁴² The corresponding eCRF should be completed.

Physical Examination

A complete physical examination will be performed at the designated study visits as specified in [Appendix E](#). The physical examination at the Baseline Visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted by the Investigator at Baseline prior to the first dose of study drug will be recorded in the subject's medical history. Abnormalities noted after the first dose of study drug will be evaluated and documented by the Investigator as to whether or not the abnormality is an AE. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

12-Lead ECG

A resting 12-lead ECG will be performed at the designated study visits as specified in [Appendix E](#). A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. ECG with QT interval corrected for heart rate using Friedericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed. In these cases, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, 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 site monitor 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 source documentation is available and provided nothing has changed in the subject's medical history to warrant a repeat test. If there are other findings that are clinically significant, the Investigator must contact the AbbVie TA MD 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.

CXR

A CXR (AP and lateral views) is required:

- For all subjects at Screening 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 CXR (posterior-anterior and lateral views) within 90 days of Screening, provided all source documentation is available at the site as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test.
- Annually for subjects with TB risk factors as identified by the TB risk assessment form ([Appendix G](#)) for subjects living in areas endemic for TB or for subjects with newly positive PPD and/or QuantiFERON-TB Gold test.

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

A radiologist or qualified physician must perform an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the Principal Investigator or their 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 should contact the AbbVie TA MD before enrolling the subject.

Spine and Pelvis X-rays

Detailed instructions for performing and transmitting the study-related x-rays of spine and pelvis are provided in a separate Imaging Acquisition Guideline (IAG)/Site Operations Manual.

Handling of X-rays of Spine and Pelvis at Screening

Screening x-rays of spine (lateral views of cervical and lumbar spine) and pelvis (AP view) must be performed within the 35-day screening period. The lateral spine x-rays will be centrally read; subjects with total spinal ankylosis are not eligible for this study. The AP pelvis x-ray will also be centrally read to evaluate the SI joints for the presence of sacroiliitis consistent with AS based on the modified New York Criteria for AS ([Appendix C](#)).

The x-rays of the spine and pelvis will not be required during the Screening Period if the subject had a previous AP pelvis x-ray and lateral spine x-rays within 90 days of the Screening Period, provided that the x-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.

X-rays will be sent to the central imaging laboratory designated by the Sponsor. Digitalized images are acceptable, provided that they meet the specifications outlined in the IAG/Site Operations Manual. X-rays not meeting the quality requirements must be repeated within the 35-day screening window. The AP pelvis x-ray will be read by the central imaging vendor solely to evaluate the SI joints for the presence of sacroiliitis consistent with AS based on the modified New York Criteria for AS, while the x-rays of the spine will be read by the central imaging vendor only for the purposes of scoring for radiographic progression. Subjects can only receive first dose of study drug after the x-rays have been centrally read and sacroiliitis is confirmed.

Screening x-rays of spine and pelvis will serve as baseline x-rays for scoring purposes.

Handling of X-rays of Spine after Baseline

X-rays of the spine will be obtained at the Week 104 Visit (end of study). If a subject prematurely discontinues the study and/or study drug, depending on the time of discontinuation, new x-rays of the spine may be needed.

- Subjects who prematurely discontinue from the study and/or study drug before Week 76 will not have x-rays performed at the PD Visit.
 - If the subject continues study participation, the subject will follow the regular visit schedule, and an x-ray will be performed at the Week 104 Visit.
- Subjects who prematurely discontinue from the study and/or study drug at or after Week 76 will have x-rays performed at the PD Visit.
 - If the subject continues study participation, the subject will follow the regular visit schedule, but an x-ray will not be performed at the Week 104 Visit.

The x-rays of the spine will be read by the central imaging vendor only for the purposes of scoring for radiographic progression.

MRI of Spine and SI Joints

All subjects who meet eligibility criteria will have an MRI evaluation of the SI joints, as well as the cervical, thoracic, and lumbar regions of the spine, prior to or at the Baseline Visit, the Week 14 Visit, as well as the Week 104 Visit. If a site is unable to obtain the MRI prior to Baseline Visit, a window of 3 days post-dose will be allowed. For the MRI at Week 14, a window of -7 days/+ 3 days will be allowed; for the MRI at Week 104, a window of ± 7 days will be allowed. If subject has a contraindication for MRI prior to enrollment, the site must discuss with the AbbVie TA MD.

Note: If the central imaging vendor confirms a negative 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.

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 MRI will only be assessed by the imaging vendor for bone marrow edema.

Note: Site staff should schedule the Week 14 MRI during the Baseline visit, if possible. For subjects who prematurely discontinue from the study drug for any reason, the site should attempt to reschedule the MRI within 2 weeks (14 days) of the PD Visit. If the MRI cannot be rescheduled within 14 days of the PD Visit, the MRI will be considered missed.

Low-Dose Computer Tomography (CT) Scan of Spine

Subjects at select sites who consent to participate in the low-dose CT scan substudy and meet eligibility criteria will have low-dose CT scan evaluation of the whole spine (cervical, thoracic, and lumbar spine) prior to or at the Baseline Visit, Week 52, and Week 104. If a site is unable to obtain the low-dose CT of the whole spine prior to Baseline Visit, a window of 2 weeks (14 days) post-dose will be allowed. Images will be sent to the central imaging vendor designated by the Sponsor. Procedures for performing and shipping the CT scans are provided in a separate manual. The low-dose CT scans will only be assessed and scored by the central imaging vendor for syndesmophytes.

Note: For subjects participating in the low-dose CT scan substudy who prematurely discontinue from the study drug for any reason prior to Week 104 but after Week 76 should have a CT scan performed at or within 2 weeks of the PD Visit.

Note for the X-rays, MRI and Low-Dose CT Scan

The central imaging vendor will assess x-rays of the sacroiliac joints and the spine, MRI of the sacroiliac joints and the spine, and low-dose CT scans only for the purposes

indicated above and will not assess for any other clinically significant findings. The investigator will be responsible for assessing the images for any clinically significant findings that may impact subject health.

TB Testing/TB Prophylaxis

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB. Expert consultation for the evaluation and/or management of TB may be considered per Investigator discretion.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form ([Appendix G](#)) and tested for TB infection by QuantiFERON-TB Gold test (or IGRA equivalent). The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF.

- Subjects with a negative TB test and CXR not suggestive of active TB or prior TB exposure may be enrolled. If a subject had a negative QuantiFERON-TB Gold (or IGRA equivalent) within 90 days prior to Screening and source documentation is available, the test does not need to be repeated provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TAMD.
- If a subject had a negative PPD Skin Test (also known as a TB Skin Test or Mantoux Test) within 90 days prior to Screening and a QuantiFERON-TB Gold test (or IGRA equivalent) cannot be performed by Central Lab at Screening and source documentation is available, TB testing by PPD Skin Test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TAMD. The results of the TB test(s) will be retained at the site as the original source documentation.
- Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with no

signs or symptoms and a CXR not suggestive of active TB may be enrolled after initiation of TB prophylaxis (see below).

- Subjects with evidence of active TB must not be enrolled.

For subjects with a negative TB test result at Screening (or the most recent evaluation), an annual TB follow-up test will be performed. If an annual TB test is newly positive (seroconversion), a CXR needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Any positive TB screen after the subject has started the study should be reported as an AE of latent TB or active TB (as applicable).

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case (including the TB test results) must be discussed with the AbbVie TA MD.

TB Testing

Additional information regarding TB testing is as follows:

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD Skin Test are not required to repeat either test at Screening or during the study and should be considered positive.
- For regions that require both PPD and QuantiFERON-TB Gold testing, both will be performed. If either PPD or QuantiFERON-TB Gold results are positive, the TB test is considered positive.
- The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines).
 - The PPD should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration, and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm," not "negative." Subjects who had an ulcerating

reaction to the PPD in the past should not be re-exposed, and the PPD should be considered positive.

- If only a PPD is placed at Screening, then the TB test to be used for the remainder of the study for that subject is the PPD. Similarly, if a subject enters the study with a QuantiFERON-TB Gold test (or equivalent) alone, then the subject should have their annual TB test performed with a QuantiFERON-TB Gold test.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the subject is considered to be negative.

For sites participating from 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 travel to, reside in, or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of the QuantiFERON-TB Gold test and/or PPD skin test (or IGRA equivalent such as T-SPOT TB test) and the CXR and has to give his/her opinion about the eligibility of each subject to be enrolled to the study. This opinion must be documented in writing in the subject's source documents.
- All subjects with a positive QuantiFERON-TB Gold test and/or PPD test (or IGRA equivalent such as T-SPOT TB test) and a CXR not suggestive of active TB need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie TA MD, and all such subjects need to receive prophylaxis for latent TB. Under no circumstances can a subject with a positive QuantiFERON-TB Gold test and/or PPD test (or IGRA equivalent

such as T-SPOT TB test) result and no prior history of treatment for active or latent TB be allowed into this trial.

TB Prophylaxis

At Screening, if the subject has evidence of latent TB infection, prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). At least 6 months of prophylaxis (or per local guidelines, whichever is longer) need to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Note: Rifampicin and Rifapentine Are Not Allowed for TB Prophylaxis

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment. For subjects with completion of a full course of anti-TB therapy but insufficient documentation, the investigator should consult with the AbbVie TA MD.

During the study, subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines and complete at least 6 months of prophylaxis (or per local guidelines, whichever is longer). TB prophylaxis should be initiated, and study drug should not be withheld. Two to 4 weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms, as well as laboratory assessment of toxicity to TB prophylaxis. Newly initiated prophylactic treatment should be captured in the eCRF and in the source documents. Prior therapy should be captured in the eCRF.

Pregnancy Test

A serum pregnancy test will be performed for all women of childbearing potential at the Screening Visit. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility. If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

In Period 1, a urine pregnancy test will be performed for all women of childbearing potential at the Baseline Visit prior to the first dose of study drug and at all subsequent visits. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld, and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started. If the serum pregnancy test is positive, study drug must be withheld, and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required.
- If a post-baseline urine pregnancy test is positive, study drug needs to be temporarily discontinued, and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be restarted. If the serum pregnancy test is positive, study drug must be permanently discontinued.

In Period 2, for women of childbearing potential, a urine pregnancy test will be performed at all visits and monthly at home between scheduled study visits. The results of the monthly at home tests will be communicated to the site. If a urine pregnancy test is positive, the subject must stop dosing, come in to the clinic, and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory.

At each visit, the study staff should review the pregnancy avoidance recommendations with each subject of childbearing potential and male subjects with a partner of childbearing potential and document this discussion in the subject's source records.

A pregnant or breastfeeding female will not be eligible for participation in this study or be allowed to continue study drug.

Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests listed in [Table 2](#). Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per Investigator's discretion. A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

The central laboratory chosen for this study will provide instructions regarding the collection, processing, and shipping of these samples.

Blood samples will be obtained for the laboratory tests at visits specified in [Appendix E](#). Blood draws should be performed only after all clinical assessments, questionnaires, and vital sign determinations are obtained.

For clinic visits where samples for serum chemistry tests are collected, subjects should be fasting (a minimum 8-hour fast) whenever possible. If a subject is not able to fast when necessary due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

Urine samples will be obtained for urinalysis testing at visits specified in [Appendix E](#). The central laboratory will be responsible for performing a macroscopic urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses, defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose

greater than normal, will be followed up with a microscopic analysis at the central laboratory.

For any laboratory test value outside the reference range that the Investigator considers to be clinically significant, the Investigator should apply the standard of care for medical evaluation and treatment per local guidelines:

- The Investigator will repeat the test to verify the out-of-range value.
- The Investigator will follow the out-of-range value to a satisfactory clinical resolution.

A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an AE.

Table 2. Clinical Laboratory Tests

Hematology (Central Lab)	Clinical Chemistry ^a (Central Lab)	Urinalysis ^b (Central Lab)	Other Laboratory Tests
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Reticulocyte count Platelet count	BUN Creatinine Total bilirubin INR (reflex only) ^c ALT AST Alkaline phosphatase CPK Sodium Potassium Chloride Bicarbonate Calcium Inorganic phosphate Uric acid Cholesterol LDL-C HDL-C Total protein Glucose Triglycerides Albumin	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocytes Nitrites Microscopic examination, if needed	<u>Central Lab Tests:</u> Serum pregnancy (bHCG) test ^d HBs Ag ^e HBs Ab ^e HBc Ab ^e HBV DNA PCR reflex only ^e HCV Ab ^e HCV RNA reflex only ^e HIV ^f QuantiFERON-TB Gold ^g hsCRP ^h FSH ^{e,i} beta-D-glucan ^j HLA-B27 ^k Lymphocyte subsets ^l <u>Local Lab Tests</u> ESR Urine pregnancy test ^m

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bHCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hsCRP = high sensitivity C-reactive protein; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; NK = natural killer; NKT = natural killer T; PCR = polymerase chain reaction; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell

- Minimum 8-hour fast. If a subject is not able to fast when necessary due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- A urine dipstick macroscopic 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 leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal.
- INR will only be measured if ALT and/or AST > 3 × ULN.
- A serum pregnancy test will be performed for all women of childbearing potential at the Screening Visit and if post-baseline urine pregnancy test turns positive.
- At Screening only.

Table 2. Clinical Laboratory Tests (Continued)

- f. Anti-HIV Ab will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health, and subject should receive or be referred for clinical care promptly. 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.
- g. If PPD not performed.
- h. The hsCRP results after Baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, or the subject. hsCRP will be performed by the Central Lab. Local laboratory or site testing for hsCRP or CRP is not allowed after Baseline. Results of tests such as hsCRP may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. As such, local hsCRP testing should not be performed until the last subject completes Period 1.
- i. At Screening for female subjects < 55 years old.
- j. At Screening for subjects in Japan only.
- k. At Baseline only.
- l. Blood samples will be collected to assess the effects of upadacitinib inhibition on lymphocyte subsets including but not limited to T (CD4+ and CD8+) cells, B (CD19+) cells, NK cells, and NKT cells. These tests will be performed by the Central Lab.
- m. A urine pregnancy test will be performed for all women of childbearing potential at the Baseline Visit prior to the first dose of study drug and all subsequent visits. If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld, and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be withheld, and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required ≥ 3 days later to document continued lack of a positive result, and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results. If a post-baseline urine pregnancy test is positive, study drug needs to be temporarily discontinued, and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be permanently discontinued.

Hepatitis Screen

All subjects will be tested for the presence of HBV and HCV at Screening. In addition, HBV and HBC testing will be performed at the designated study visits as specified in [Appendix E](#) for subjects in Japan.

Hepatitis B

Subjects will be tested for the presence of HBV at Screening using the following tests:

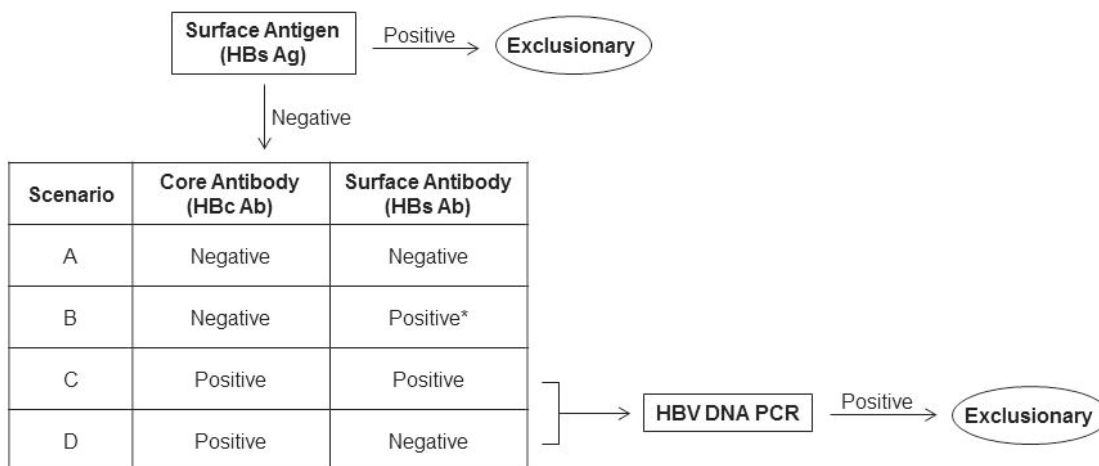
- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will be tested (automatic reflex testing) for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

- A negative test result for HBc Ab does **not** require HBV DNA PCR qualitative testing, and the subject may be enrolled (Figure 2, Scenarios A and B).
- For a subject who has had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected, and the subject may be enrolled (Figure 2, Scenario B).*
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 2, Scenarios C and D; For Japan only: including Scenario B).
 - A result that exceeds the detection sensitivity of the central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
 - A subject with a negative result for HBV DNA may be enrolled.

Figure 2. Criteria for HBV DNA PCR Qualitative Testing



* For subjects who have had an HBV vaccination (should be documented in the medical history), a positive test result for HBs Ab is expected, and these subjects may be enrolled. For subjects without a history of HBV vaccination (and for subjects in Japan and China), a positive result for HBs Ab/anti-HBs requires HBV DNA PCR testing.

For subjects in Japan: Subjects with positive HBs Ab and/or positive HBc Ab results should have HBV-DNA PCR test performed at the specified visits ([Appendix E](#)); in cases where recurrence of HBV-DNA is observed, the subject should be discontinued from the study. This measure is not necessary in subjects with history of HBV vaccination and positive HBs Ab result.

Hepatitis C

Blood samples for Hepatitis C serology will be obtained at the Screening Visit. A subject will not be eligible for study participation if test results indicate active Hepatitis C (HCV RNA detectable in any subject with anti HCV Ab).

HIV

Subjects with a known history of HIV infection are excluded from study participation. Anti-HIV Ab will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report these

results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health, and subject should be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate an HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Other Laboratory Assessments

hsCRP

Blood samples for hsCRP will be obtained at visits specified in [Appendix E](#). The hsCRP results after Baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, or the subject. hsCRP will be performed by the Central Lab. Local laboratory or site testing for hsCRP or CRP is not allowed after Baseline. Results of tests such as hsCRP may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. As such, local hsCRP testing should not be performed until the last subject completes Period 1.

Lymphocyte Subsets

Blood samples will be collected at visits specified in [Appendix E](#) to assess the effects of ABT-494 inhibition on lymphocyte subsets including but not limited to T (CD4+ and CD8+) cells, B (CD19+) cells, NK cells, and NKT cells. These tests will be performed by the Central Lab.

Subject Questionnaires

Subjects will complete the following questionnaires as specified in [Appendix E](#); a validated translation will be provided in their local language, as applicable:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)^{43,44}
- Bath Ankylosing Spondylitis Functional Index (BASFI)^{44,45}

- Patient's Global Assessment of Disease Activity (PtGA)^{44,46}
- Patient's Assessment of Total Back Pain⁴⁴
- Patient's Assessment of Nocturnal Back Pain^{44,46}
- Patient's Global Assessment of Pain⁴⁷
- Ankylosing Spondylitis Quality of Life (AS QoL)^{48,49}
- ASAS Health Index (HI)⁵⁰
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)⁵¹
- Insomnia Severity Index (ISI)^{52,53}
- Work Productivity and Activity Impairment (WPAI)⁵⁴

All patient-reported outcomes (PROs) will be collected electronically. The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

Tender Joint Count (TJC) and Swollen Joint Count (SJC) Assessment

TJC Assessment

An assessment of 68 joints will be done for tenderness by pressure manipulation on physical examination at visits specified in [Appendix E](#). Joint pain/tenderness will be classified as: present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA").

SJC Assessment

An assessment of 66 joints will be done by directed physical examination at visits specified in [Appendix E](#). The joints to be examined for swelling are the same as those examined for tenderness, except the hip joints are excluded. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA"). Any injected joint will be classified as "no assessment" ("NA") for 90 days from the time of the intra-articular injection.

If possible, the TJC and SJC should be performed by an independent and blinded joint assessor who should not perform any other study-related procedures.

In order to minimize variability, the same independent joint assessor should evaluate the subject at each visit for the duration of the trial as much as possible. A back-up independent joint assessor should be identified. The independent joint assessors should be qualified medical professionals (e.g., nurse, physician's assistant, physician). Any other joint assessor must be trained and competent in performing such assessments. It is the responsibility of the Investigator to ensure that all assessors are qualified and trained to perform joint assessments. If the independent assessor is not available, the pre-identified back-up assessor should perform such assessments.

Dactylitis

An evaluation will be conducted at the visits specified in [Appendix E](#) to assess the presence or absence of dactylitis in all 20 of the subjects' digits. The assessment should begin with visual inspection of the hands and feet. For each pair of digits in which one or both digits appear dactylitic, the circumference of the affected digits (both right and left side) will be assessed using a dactylometer. Additionally, the affected digit pairs will be assessed for tenderness by squeezing the digital shaft mid-way between the metacarpophalangeal and proximal interphalangeal joints and will be recorded as tenderness, yes or no. Tenderness should not be assessed by squeezing the joint lines. If a digit is missing and its contralateral digit is dactylitic, "digit absent" will be recorded for the missing digit. For any digit without an available dactylometer measurement, the standard reference value will be utilized in calculation of the Leeds Dactylitis Index.⁵⁵ The standard reference values will not be entered into the eCRF. A dactylometer will be provided to sites for use. Digits injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

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

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

The BASMI_{lin} will be conducted at the visits specified in [Appendix E](#) to evaluate spinal mobility in a subject.⁵⁶

The 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 (MASSES)

The MASSES evaluation will be conducted at the visits specified in [Appendix E](#) to assess the presence or absence of enthesitis at 13 different sites (first costochondral joint left/right, seventh costochondral joint left/right, posterior superior iliac spine left/right, anterior superior iliac spine left/right, iliac crest left/right, fifth lumbar spinous process, and proximal insertion of Achilles tendon left/right), noting the subjects' responses.⁵⁷

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

Physician Global Assessment of Disease Activity (PGA)

At visits specified in [Appendix E](#), the Physician will rate global assessment of subject's current disease activity independent of the subject's self-assessment using a 0 – 10 NRS, anchored at either end by opposite adjectives.^{44,46}

ASAS 20

The ASAS 20 calculation is required at and after the Week 16 visit to determine if a subject fails to achieve ASAS 20 response. ASAS 20 response is defined as an improvement of $\geq 20\%$ and absolute improvement of ≥ 1 unit (on a scale of 0 to 10) from Baseline in at least three of the following four domains, with no deterioration (where deterioration is defined as a worsening of $\geq 20\%$ and a net worsening of ≥ 1 units [on a scale of 0 to 10]) in the remaining domain:⁵⁸

- Patient's Global Assessment – Represented by the PtGA 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 two morning stiffness related-BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10]).

ASAS 20 criteria will be calculated by Interactive Response Technology (IRT).

Randomization/Drug Assignment

All Screening laboratory results must be reviewed, signed, and dated by the Principal Investigator or Sub-investigator prior to the Baseline Visit. Subjects will not be enrolled into the study if laboratory or other Screening result abnormalities are deemed clinically significant by the Principal Investigator or Sub-investigator.

Subjects will be eligible for randomization if they continue to meet all of the selection criteria (Section 5.2) at Baseline and are willing to continue in the study.

See Section 5.5.3 for details regarding the method of assigning subjects to treatment groups.

Subject Diary

During the Baseline Visit, subjects will be dispensed a paper subject diary and will be trained on how to complete the diary by site staff. Subjects will be asked to notate their concomitant medication use and AEs and document date and times of doses of study drug taken between study visits. The subject diary will be reviewed by site personnel with the subject at each visit, and a review and description of the subject diary notations will be documented in the subject's source documentation and recorded on the applicable eCRF. Replacement diaries will be dispensed as needed should a subject misplace a subject diary. The completed diaries will be collected at the subject's final visit and maintained at the site as source documentation.

Study Drug Dispensing, Dosing, and Compliance

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in [Appendix E](#). The first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed. Subjects will maintain a dosing diary for all study drug administered outside of the study visit (i.e., at home) to capture dosing dates and times. At visits specified in [Appendix E](#), the site personnel will review and retain a copy of the dosing diary, returned study drug kits, and empty study drug packaging to verify compliance.

All relevant dosing information will be entered into the eCRF at each visit.

Refer to Section 5.5 for additional information.

5.3.1.2 Collection and Handling of Optional Samples for Exploratory Research and Validation Studies

Subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research/validation study.

Exploratory research can help to improve AbbVie's understanding of how individuals respond to drugs and the ability to predict which subjects would benefit from receiving specific therapies. In addition, exploratory research may help to improve the understanding of how to diagnose and assess/monitor AS by assessing [REDACTED]

Validation studies, including those related to the development of [REDACTED], may be carried out retrospectively in order to assess associations between [REDACTED]

AbbVie (or people or companies working with AbbVie) will store the [REDACTED] exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on upadacitinib (or drugs of this class) or AS and related conditions continues, but for no longer than 20 years after study completion.

[REDACTED] will be collected at the visits indicated in [Appendix F](#) from each subject who consents to provide samples for exploratory/validation research. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Samples will be shipped frozen to AbbVie or a designated laboratory for [REDACTED] and/or long-term storage or analyses. Instructions for the preparation and shipment of the [REDACTED] will be provided in a laboratory manual.

[REDACTED] will be collected at the visits indicated in [Appendix F](#) from each subject who consents to provide samples for exploratory/validation research. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Samples will be shipped to AbbVie or a designated laboratory for [REDACTED] and/or long-term storage or analyses. Instructions for the preparation and shipment of the samples will be provided in a laboratory manual.

[REDACTED] will be collected at the visits indicated in [Appendix F](#) from each subject who consents to provide samples for exploratory/validation research. These

samples may be used for [REDACTED] if needed. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Samples will be shipped to AbbVie or a designated laboratory for long-term storage and/or analyses. Instructions for the preparation and shipment of the samples will be provided in a laboratory manual.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for assay of upadacitinib and possibly other concomitant medications will be collected as follows:

- Weeks 2 and 4 prior to dosing;
- Weeks 8, 12, 14, 24, 52, 76, and 104/PD at any time during the visit.

On Week 2 and Week 4 visit days, if possible, subjects should take the study drug dose at the clinic after collecting the PK blood sample, except if the subjects regularly take the study drug dose at night. Those subjects who regularly take the study drug dose at night should continue to take study drug according to their normal schedule. For all other visits, subjects can take the study drug dose on visit days at their regular schedule and not necessarily at the clinic.

The date and accurate time of the PK sample collection will be recorded on the lab requisition form. The date and accurate time of the last two study drug doses will be recorded on the eCRF to the nearest minute.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.2 Measurement Methods

Plasma concentrations of upadacitinib will be determined by the Drug Analysis Department at AbbVie using a validated liquid chromatography/mass spectrometry method.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The primary endpoint is the proportion of subjects with ASAS 40 response at Week 14, which is defined as a $\geq 40\%$ improvement and an absolute improvement of ≥ 2 units (on a scale of 0 to 10) from Baseline in at least three of the following four domains, with no worsening at all in the remaining domain:

- Patient's Global Assessment – Represented by the PtGA 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 two morning stiffness-related BASDAI NRS scores (mean of items 5 and 6 of the BASDAI [0 to 10]).

5.3.3.2 Secondary Variable

The key multiplicity adjusted secondary efficacy endpoints (upadacitinib versus placebo unless noted otherwise) at Week 14 are:

1. Change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS);
2. Change from Baseline in MRI Spondyloarthritis Research Consortium of Canada (SPARCC) score (Spine);
3. Proportion of subjects with BASDAI 50 response (defined as 50% improvement in the Bath AS Disease Activity Index);

4. Change from Baseline in AS QoL;
5. Proportion of subjects with ASAS partial remission (PR) (defined as an absolute score of ≤ 2 units for each of the four domains identified in ASAS 40);
6. Change from Baseline in BASFI;
7. Change from Baseline in BASMI_{lin};
8. Change from Baseline in MASES;
9. Change from Baseline in WPAI;
10. Change from Baseline in ASAS HI.

Additional key secondary endpoints (upadacitinib versus placebo) are:

- ASAS 20 response at Week 14;
- Change from Baseline in MRI SPARCC score (SI joints) at Week 14.

5.3.3.3 Additional Variables

Additional endpoints are the following measurements assessed in subjects treated with upadacitinib versus placebo at scheduled time points other than those specified for the primary and key secondary variables:

- Proportion of subjects with:
 - ASAS 20 response;
 - ASAS 40 response;
 - ASAS PR;
 - ASAS 5/6 (20% improvement from Baseline in five out of the following six domains: BASFI, patient's assessment of total back pain, PtGA, inflammation [mean of items 5 and 6 of the BASDAI] lateral lumbar flexion from BASMI_{lin}, and high sensitivity CRP [hsCRP]);
 - ASDAS Inactive Disease (ASDAS score < 1.3);
 - ASDAS Major Improvement (change from Baseline at least 2.0);

- ASDAS Clinically Important Improvement (change from Baseline of at least 1.1).
- Change from Baseline in:
 - ASAS HI;
 - ASDAS;
 - AsQoL;
 - BASDAI;
 - BASFI;
 - BASMI_{lin};
 - CRP;
 - Dactylitis;
 - FACIT-F;
 - ISI;
 - MASES;
 - Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) score with conventional radiograph;
 - MRI SPARCC score of SI joints;
 - MRI SPARCC score of Spine;
 - Patient's Assessment of Total Back Pain;
 - Patient's Assessment of Nocturnal Back Pain;
 - Patient's Global Assessment of Pain;
 - PGA;
 - PtGA;
 - TJC and SJC;
 - WPAI.

Evaluation of structural changes in the spine will be explored in subjects who are participating in the low-dose CT scan substudy using a scoring system for syndesmophytes.

5.3.4 Safety Variables

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

5.3.5 Pharmacokinetic Variables

Plasma upadacitinib concentrations will be obtained at the times indicated in [Appendix E](#). A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of upadacitinib oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

5.3.6 Exploratory Research Variables and Validation Studies

Optional samples may be collected to conduct exploratory investigations into [REDACTED]. The types of [REDACTED] to be analyzed may include but are not limited to [REDACTED].

[REDACTED] may be used to assess and generate [REDACTED]. These assessments may be explored in the context of [REDACTED]. The results from these analyses are exploratory in nature and may not be included with the clinical study report (CSR).

The samples may also be used to [REDACTED]. In addition, samples from this study may be stored for future use. Samples may then be used to validate [REDACTED].

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Subjects can request to be discontinued from participating in the study at any time for any reason, including but not limited to lack of response to treatment. The Investigator may discontinue any subject's participation for any reason, including an AE, safety concerns, lack of efficacy, or failure to comply with the protocol. See Section 6.1.7 for toxicity management criteria.

Subjects will have study drug treatment discontinued immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs that rule out continuation of the study drug, as determined by the Investigator or the AbbVie TA MD.
- Serious infections (e.g., sepsis) that cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk for continued participation in the trial as determined by the Investigator.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion or exclusion criteria violation was noted after the subject started the study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie TA MD.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in situ of the cervix.

- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation as determined by the Investigator.
- Subject develops a gastrointestinal perforation.
- Subjects not responding to treatment are to be withdrawn from the trial based on Investigator's discretion.
- Starting at Week 24, subjects who still do not achieve at least an ASAS 20 response at two consecutive visits will be discontinued from study drug treatment.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis.

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should complete a PD visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should continue to be followed for all regularly scheduled visits as outlined in [Appendix E](#) and adhere to all study procedures except for dispensing study drug, PK sample collection, blood sample collection for optional exploratory research and validation studies, and x-rays. (New x-rays are dependent on the time of discontinuation; refer to Section 5.3.1.1 for details.) In addition, all future efficacy-driven discontinuation criteria no longer apply (ASAS 20 response). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks. In addition, a 30-day follow-up visit (or phone call if a visit is not possible) should occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. Subjects who discontinue the study prematurely after randomization will not be replaced.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information

will be recorded on the appropriate eCRF page. 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 study drug, the subject will be treated in accordance with the Investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

Lost to Follow-Up

For subjects to be 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 and documented in the subject's source documentation.

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

Study drug will be taken orally QD, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day. The study drug can be taken with or without food.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in [Table 3](#).

Table 3. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABT-494	oral	tablet	15 mg	AbbVie
ABT-494 placebo	oral	tablet	NA	AbbVie

5.5.2.1 Packaging and Labeling

ABT-494 and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the kits. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug

ABT-494 must be stored at controlled room temperature (15° to 25°C/59° to 77°F). Study drug must not be frozen at any time. The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be randomized using IRT. Before the study is initiated, IRT directions will be provided to each site.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects that re-screen, the Screening number assigned by the IRT at the initial Screening visit should be used; a new Screening number should not be requested.

Subjects will be eligible for randomization if they continue to meet all of the selection criteria (Section 5.2) at Baseline and are willing to continue in the study.

Subjects will be randomized in a 1:1 ratio using IRT to receive double-blind study drug in one of the following treatment groups:

- Group 1: Upadacitinib 15 mg QD (n = 85)
- Group 2: Placebo (n = 85)

Randomization will be stratified by Screening hsCRP (\leq ULN vs. $>$ ULN) and geographic region (US/Canada, Japan, RoW). Subjects who were randomized to placebo at Baseline will receive upadacitinib 15 mg QD in an open-label manner at Week 14.

The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the Statistics Department at AbbVie.

IRT will provide the appropriate study drug kit number(s) to dispense to each subject. Study drug will be administered at the study visits as summarized in Section 5.3.1.1. Returned study drug should not be re-dispensed to any subject.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in Section 5.5.1.

On dosing days that occur on study visit days, subjects should follow the regular dosing schedule (refer to Section 5.3.2.1 regarding Week 2 and Week 4 visits).

Each subject's dosing schedule should be closely monitored by the site at each study visit by careful review of the subject's dosing diary. This will ensure that all subjects enrolled into the study maintain their original dosing schedule beginning with the first dose of study drug (Baseline/Day 1).

If a subject should forget to take their upadacitinib (or matching placebo) dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time. If the subject experiences a study drug interruption > 7 consecutive days during Weeks 1 through 14 (Period 1) or > 30 consecutive days during Period 2 they should notify the Investigator, and the Investigator will decide if study drug should be restarted.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment throughout Period 1. The Investigator, study site personnel, and the subject will remain blinded to each subject's treatment assignment in Period 1 throughout the study. In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of medical emergency.

In the event of a medical situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary that warrants breaking the blind prior to contacting the AbbVie TA MD, the Investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the Investigator. If the IRT system is unavailable, unblinding may occur by contacting EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: <http://www.endpointclinical.com/help-desk/>. In the event that the blind is broken before notification to the AbbVie TA MD, it is requested that the AbbVie

TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

The primary analysis will be conducted after all subjects have completed Week 14 or have prematurely discontinued prior to Week 14. Study sites and subjects will remain blinded to the treatment assignment in Period 1 for the duration of the entire study.

5.5.5.2 Blinding of Data for Data Monitoring Committee (DMC)

An external Data Monitoring Committee (DMC) comprised of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, and relevant safety data to be assessed.

Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

As of 18 April 2019, with all subjects having reached the end of Period 1, and after final review of unblinded safety data, the DMC concluded its oversight of this study.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Subject dosing will be recorded on a subject dosing diary. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. The study site personnel will document compliance in the study source documents.

5.5.7 Drug Accountability

The Investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document and by registering the arrival of drug through the IRT. The original Proof of Receipt Note and the IRT confirmation sheet will be kept in the site files as a record of what was received.

In addition, an IRT will be used to document investigational product accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number, and the identification of the person dispensing the drug.

All empty/used study drug packaging will be inventoried by the site and verified by the site monitor. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary. Empty/used packaging will be retained (unless prohibited by local law) until the site monitor is on site to confirm the returned study drug. Site monitor(s) and site staff will complete study drug accountability via IRT, source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible. After drug accountability has been completed, used packaging and unused study drug will be destroyed on site according to local procedures or regulations or returned to the destruction depot by the site monitor (for those sites that do not meet AbbVie's documentation requirements for on-site destruction). The use of a third party vendor for drug destruction must be pre-approved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This study is a Phase 2 study with the quality and rigor of a Phase 3 study. Therefore, it is classified as a Phase 2/3 study. The study has 90% power on the primary efficacy

endpoint and is well-controlled, with randomization, blinded intervention, high-quality trial conduct, unbiased data analysis and interpretation, and rigorous control of the overall type I error rate, to provide scientifically sound data evidence in efficacy and safety.

This study includes two periods:

Period 1 is a 14-week, randomized, double-blind, placebo-controlled period to compare safety and efficacy of upadacitinib versus placebo in subjects with a clinical diagnosis of AS and meeting the modified New York Criteria for AS who have an inadequate response to or intolerance or contraindication for NSAIDs and are bDMARD-naïve. Period 1 is designed to test superiority of upadacitinib versus placebo for achieving the primary endpoint (ASAS 40 response rate) at Week 14 and other secondary efficacy parameters. A comparative study utilizing a placebo-control design provides an unbiased assessment of the efficacy and safety profile of upadacitinib.

The purpose of **Period 2** is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects who have completed Period 1. Subjects will continue to receive upadacitinib 15 mg QD per original randomization assignment in an open-label manner. Subjects who were randomized to placebo at Baseline will receive open-label upadacitinib 15 mg QD at Week 14.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with AS. All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

The intended study population is active AS patients who have had an inadequate response to at least two NSAIDs over an at least 4-week period in total at maximum recommended or tolerated doses or intolerance to or a contraindication for NSAIDs as defined by the

Investigator, and who are bDMARD-naïve. The specific population chosen was based on the unmet medical need of these subjects. Key entry criteria are to enroll adult female and male subjects who are at least 18 years of age with a clinical diagnosis of AS and meet the modified New York Criteria for AS. Eligible study subjects must have a BASDAI score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 – 10 NRS at the Screening and Baseline Visits. Subjects who enter the study on permitted concomitant medications(s) must have been on a stable dose for the amount of time specified in the inclusion criteria (Section 5.2.1) prior to the first dose of study drug.

5.6.4 Selection of Doses in the Study

This Phase 2/3 study will evaluate a single dose of upadacitinib 15 mg QD using the once-daily tablet formulation.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Data from the tofacitinib Phase 2b study in AS demonstrated that tofacitinib 5 mg BID and 10 mg BID demonstrated greater clinical efficacy versus placebo in reducing the signs, symptoms, and objective measures of the disease.²⁵ The 15 mg QD dose of upadacitinib is expected to be comparable to or better than the 5 mg BID dose of tofacitinib. The dose to be evaluated in this study is predicted to provide exposures that are lower than the No-Observed-Adverse-Effect-Level (NOAEL) exposures from the preclinical toxicology studies as well as the highest exposures that were previously evaluated and found to be safe and well tolerated in healthy volunteers in Phase 1 and in subjects with RA in Phase 2.

Therefore, the dose selected for Study M16-098, upadacitinib 15 mg QD dosed for up to 104 weeks, is expected to be efficacious with an acceptable safety profile.

6.0 Complaints

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

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For AEs, please refer to Section 6.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

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

All AEs will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An 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 AE 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 AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from

the study drug, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE 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 AE.

6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an 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 SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF.

6.1.1.3 Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study (see detailed toxicity management in Section 6.1.7):

- Serious infections
- Opportunistic infections
- Malignancy
- Non-Melanoma Skin Cancer (NMSC)
- Malignancy excluding NMSC
- Lymphoma
- Hepatic Disorder
- Gastrointestinal Perforations
- Anemia
- Neutropenia
- Lymphopenia

- Herpes Zoster
- Rhabdomyolysis/myopathy
- Creatine Phosphokinase (CPK Elevation)
- Renal Dysfunction
- Tuberculosis
- Adjudicated cardiovascular events
- Embolic and thrombotic events (non-cardiac, non-CNS)

6.1.2 Adverse Event Severity

When criteria are available, events should be graded as described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.⁶⁰

If guidance for specific events is not available, grading should be as follows:

Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate (Grade 2): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL; instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Severe (Grade 3 – 5):

- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
- Life-threatening consequences; urgent intervention indicated;
- Death related to AE.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

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

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.

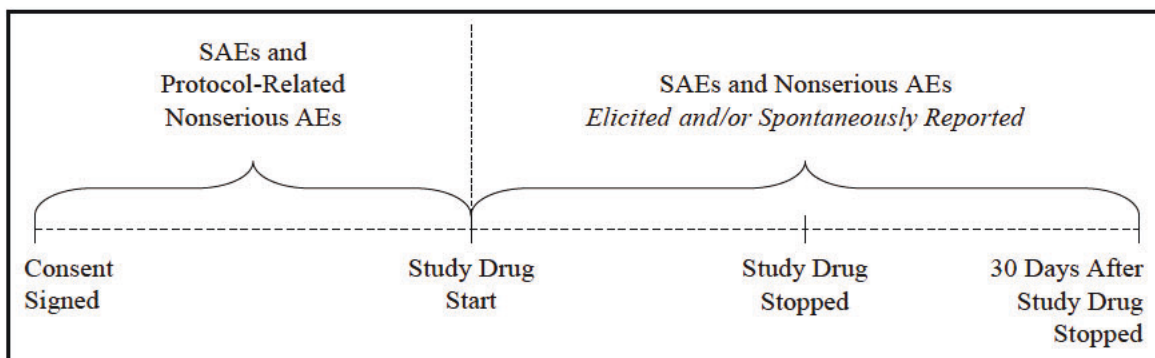
If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the Investigator for the SAE.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. Subjects who discontinue study drug treatment but continue to participate in the study will have SAEs and nonserious AEs collected for the remainder of study participation. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signed the study-specific informed consent.

AE information will be collected as shown in [Figure 3](#).

Figure 3. Adverse Event Collection



Additionally, in order to assist the adjudication process, additional information on any potential cardiovascular events will be collected, if applicable. In the case of any of the following reported events, the supplemental cardiovascular events eCRF should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack.

In the case of a reported AE of herpes zoster infection or embolic and thrombotic event (non-cardiac, non-CNS), a Supplemental AE eCRF should also be completed.

6.1.5 Adverse Event Reporting

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE[®] system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: [REDACTED]

FAX to: [REDACTED]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team

[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Office: [REDACTED]

Email: [REDACTED]

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

Primary TA MD:

[REDACTED]
AbbVie Inc.

[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [REDACTED]

Mobile: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline, where calls will be re-directed to a designated backup AbbVie TA MD:

Phone: [REDACTED]

The Sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local regulations. The reference document used for SUSAR reporting in the European Union (EU) countries will be the most current version of the Investigator's Brochure.

In Japan, the Principal Investigator will provide documentation of all SAEs to the Director of the investigative site and the Sponsor.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject or the partner of an enrolled subject, including the outcome of the pregnancy, will be collected. Pregnancies in study subjects and their partners will be identified from the date of the first dose of study drug through 30 days following the last dose of study drug, and the pregnancy will be followed to outcome.

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.

In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome.

6.1.7 Toxicity Management

The toxicity management of the AEs, including AEs of special interest, consists of safety monitoring (review of AEs on an ongoing basis and periodical/ad hoc review of safety

issues by a safety data monitoring committee), interruption of study drug dosing with appropriate clinical management if applicable, and discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

Note: For subjects who discontinued study drug but continue study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central lab), and any intolerability to standard of care therapies should be managed by the prescribing physician.

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Re-challenge with study drug may occur once the infection has been successfully treated. If study drug has been interrupted for a serious infection for more than 14 consecutive days during Period 1 of the study or 30 consecutive days thereafter, the subject must inform the Investigator and the Investigator can determine if study drug can be restarted. Subjects who develop active TB must be discontinued from study drug.

Herpes Zoster: If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a gastrointestinal perforation should be evaluated promptly for early diagnosis and treatment. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued from study drug.

Cardiovascular Events (MACE): Subjects presenting with potential cardiovascular events should be appropriately assessed and carefully monitored. These events will be

reviewed and adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner (Section 6.1.9).

Malignancy: Subjects who develop malignancy other than NMSC or carcinoma in-situ of the cervix must be discontinued from study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at increased risk for skin cancer.

Thrombosis Events: Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug OR a confirmed absolute QTcF value > 500 msec.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject and apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values (confirmation by repeat testing is required) are described in Table 4 and may require an appropriate supplemental eCRF be completed. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	<ul style="list-style-type: none"> • If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the Investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	<ul style="list-style-type: none"> • If confirmed < 1000/μL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its baseline value. • Discontinue study drug if confirmed < 500/μL by repeat testing with new sample.
Absolute lymphocyte counts (ALC)	<ul style="list-style-type: none"> • If confirmed < 500/μL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its baseline value.
Total white blood cell count	<ul style="list-style-type: none"> • If confirmed < 2000/μL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its baseline value.
Platelet count	<ul style="list-style-type: none"> • If confirmed < 50,000/μL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	<ul style="list-style-type: none"> • Discontinue study drug if confirmed ALT or AST $> 3 \times$ ULN by repeat testing with new sample and either a total bilirubin $> 2 \times$ ULN or an international normalized ratio > 1.5. <ul style="list-style-type: none"> ○ INR will only be measured in subjects with ALT or AST $> 3 \times$ ULN by the central lab by reflex testing and confirmation is not needed for consideration in toxicity management criteria. • Discontinue study drug if confirmed ALT or AST $> 3 \times$ ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$). • Discontinue study drug if confirmed ALT or AST $> 8 \times$ ULN by repeat testing with new sample. • Discontinue study drug if confirmed ALT or AST $> 5 \times$ ULN by repeat testing with new sample for more than 2 weeks. <p>For all of the above ALT or AST elevation scenarios, complete supplemental hepatic eCRF.</p>
Serum Creatinine	<ul style="list-style-type: none"> • If serum creatinine is $> 1.5 \times$ the baseline value and $> \text{ULN}$, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to $\leq 1.5 \times$ baseline value and $\leq \text{ULN}$. • If confirmed serum creatinine $\geq 2 \text{ mg/dL}$, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. <p>For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.</p>
Creatine Phosphokinase	<ul style="list-style-type: none"> • If confirmed CPK value $\geq 4 \times \text{ULN}$ and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If confirmed CPK $\geq 4 \times \text{ULN}$ accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. <p>For the above CPK elevation scenarios, complete supplemental CPK eCRF.</p>

For allowed study drug interruption, the following rules apply:

Period 1

- Allow study drug interruption up to 7 consecutive days for AEs and emergency surgery. Elective surgery will not be allowed during this 14-week period.
- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow

reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Period 2

- Allow study drug interruption up to 30 consecutive days for AEs and emergency surgery during Period 2. PI will make determination if study drug should be restarted for interruptions > 30 days.
- If the subject undergoes elective surgery, the study drug should be interrupted 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.1.8 Data Monitoring Committee

An external DMC will review unblinded safety data. See Section 5.5.5.2 for details.

6.1.9 Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular AEs in a blinded manner as defined by the Cardiovascular Adjudication Committee charter.

6.2 Product Complaint

6.2.1 Definition

A product complaint is any complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

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

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

6.2.2 Reporting

Product complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint Form. Product complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The Principal Investigator is responsible for complying with all protocol requirements and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying

IEC/IRB regulatory authorities (as applicable) and the following AbbVie Clinical Contact:

Primary Contact:



Office:
Fax:
Email:



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.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The primary analysis will be conducted after all subjects have completed the Week 14 visit or have prematurely discontinued prior to Week 14. The analysis will be conducted for the comparisons of the upadacitinib group versus the placebo group. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of the study.

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

database lock for the primary analysis at Week 14. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

8.1.1 Analysis Populations

8.1.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who received at least one dose of study drug. The FAS will be used for all efficacy and baseline analyses.

8.1.1.2 Per Protocol Analysis Set

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not have any major protocol violations during the study. Additional analysis may be conducted on the Per Protocol analysis set in order to evaluate the impact of major protocol violations. The Per Protocol Analysis Set will be determined prior to the Week 14 primary analysis database lock.

8.1.1.3 Safety Analysis Set

The Safety Analysis Set consists of all subjects who received at least one dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

8.1.2 Subject Accountability, Disposition and Study Drug Exposure

8.1.2.1 Subject Accountability

The following will be summarized by site and by treatment group, as well as overall: number of subjects randomized, the number of subjects who received at least one dose of study drug, the number of subjects who completed, the number of subjects who prematurely discontinued study drug, and the number of subjects who prematurely discontinued study participation.

8.1.2.2 Subject Disposition

The number and percentage of subjects who are randomized, received at least one dose of study drug, prematurely discontinued study drug, prematurely discontinued study participation, and completed will be summarized by treatment group and overall. Reasons for premature discontinuation of study drug and study participation will be summarized separately for all randomized subjects by treatment group and overall, with frequencies and percentages by reason for discontinuation.

8.1.2.3 Study Drug Exposure

Exposure to study drug will be summarized for the Safety Analysis Set. The exposure to study drug will be summarized with the mean, standard deviation, median, and range for each treatment group. The exposure to study drug is defined as the difference between the dates of the first and last doses of the study drug plus 1 day.

Study drug compliance will be summarized for each treatment group. The compliance is defined as the number of tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) during the subject's participation divided by the number of tablets a subject is supposed to take during the subject's participation.

8.1.3 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall for the FAS. For the purpose of this analysis, baseline data for each subject will be the data collected immediately prior to the first dose of study drug.

Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, and range. For discrete variables, frequencies and percentages for each category will be summarized.

Medical history will be presented in counts and percentages of subjects, broken down by Body System and Diagnosis.

Prior therapy and medication will be summarized by treatment group. Prior therapy and medication will include all therapies and medications administered prior to the date of first dose of study drug.

Concomitant medications will also be summarized with frequencies and percentages for each treatment group. All medications administered will be included.

8.1.4 Efficacy Analysis

All efficacy analyses will be carried out using the FAS population, which includes all randomized subjects who receive at least one dose of study drug.

8.1.4.1 Primary Efficacy Variables

Analysis of the primary endpoint will be conducted on the FAS based on treatment as randomized. Comparison of the primary endpoint will be made between the upadacitinib group and the placebo group using the Cochran-Mantel-Haenszel test, adjusting for main stratification factors. For the primary analysis, Non-Responder Imputation (NRI) will be used. The analysis will be repeated using Observed Cases (OC) approach. Supportive analysis will also be conducted on the Per Protocol Analysis Set.

The primary efficacy analyses will also be performed in demographic subgroups, including age, gender, race, weight, body mass index, and geographical region, to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and stratification factors will also be conducted.

8.1.4.2 Key Secondary Efficacy Variables

Unless otherwise specified, comparisons are between the upadacitinib group and the placebo group.

For binary endpoints, frequencies and percentages will be reported for each treatment group. Similar analyses as for the primary endpoint will be conducted.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Comparisons between the upadacitinib group and the placebo group will be performed using the Mixed Model for Repeated Measures (MMRM) with treatment group, visit, and treatment-by-visit interaction as fixed effects and the corresponding baseline value and the main stratification factors as the covariates.

8.1.4.3 Additional Efficacy Variables

Additional efficacy variables as listed in Section 5.3.3.3 will be summarized for all visits. For binary endpoints, frequencies and percentages will be reported by treatment group by visit. For continuous endpoints, the change from baseline mean, standard deviation, median, and range will be reported by treatment group by visit.

8.1.4.4 Multiplicity Control for the Primary and Key Secondary Endpoints

In order to preserve Type I error, a step-down approach will be used to test the primary and key secondary endpoints where statistical significance can be claimed for a lower-ranked endpoint only if the previous endpoints in the sequence meet the requirements of significance. The group of multiple endpoints (including proportion of subjects with BASDAI 50 response, proportion of subjects with ASAS partial remission, changes from baseline in AS QoL, BASFI, BASMI_{lin}, MASES, and WPAI) will be tested using the Hochberg procedure in the ranking sequence, conditional on significance of higher-ranked endpoints.

8.1.4.5 Imputation Methods

The following methods will be used for missing data imputation:

Observed Cases (OC): The OC analysis will not impute values for missing evaluations; thus, a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

Non-Responder Imputation (NRI): NRI applies to binary endpoints only. In NRI analysis, subjects who prematurely discontinue study drug will be considered non-responders on or after discontinuation date.

Mixed Model for Repeated Measures (MMRM): The MMRM includes treatment, visit, and treatment-by-visit interaction as fixed effects, and the corresponding baseline values and the main stratification factors as covariate; a covariance matrix will be used to account for the correlation structure between visits.

The NRI approach will serve as the primary analysis approach for key binary endpoints. Analysis for key binary endpoints will also be repeated using OC. The MMRM approach will serve as the primary analysis approach for key continuous endpoints.

8.1.4.6 Long-Term Efficacy

The efficacy endpoints of long-term efficacy analysis will be summarized for all visits, including visits beyond Week 14.

Long-term efficacy by time point will be summarized using descriptive statistics. For binary endpoints, frequencies and percentages will be summarized. For continuous endpoints, the mean and standard deviation will be reported.

8.1.5 Safety Analysis

8.1.5.1 General Considerations

Safety analyses will be carried out using the Safety Analysis Set. Analyses will be conducted in primary analysis at Week 14, as well as for the entire study.

Safety analyses are based on treatments actually received. Safety will be assessed by treatment-emergent adverse events (TEAEs), physical examination, laboratory assessments, and vital signs. The number and percent of subjects experiencing TEAEs by treatment group will be tabulated by the Medical Dictionary for Drug Regulatory Activities (MedDRA[®]) system organ class (SOC) and preferred terms (PT). In addition,

summary of serious AEs and TEAEs by severity and relationship to study drug as assessed by the Investigators will be provided. SAEs, severe TEAEs, or TEAEs that lead to premature study discontinuation will be listed. The changes in vital signs, physical examination results, and clinical laboratory variables at each visit as compared to baseline will be summarized. Shift of laboratory values from baseline at defined time points will be tabulated.

Missing safety data will not be imputed.

8.1.5.2 Analysis of Adverse Events

8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)

AEs will be coded using MedDRA. A TEAE is defined as AE that began or worsened in severity after initiation of study drug.

AEs starting more than 30 days following the last dose of study drug will not be included in summaries of TEAEs.

As a general safety summary, the number and percentage of subjects experiencing TEAEs will be summarized for each treatment group for the following AE categories:

- All AEs;
- All severe AEs;
- All reasonably possibly related AEs;
- All SAEs;
- Frequent AEs (reported in 5% of subjects or more in any treatment group);
- Frequent reasonably possibly related AEs (reported in 5% of subjects or more in any treatment group);
- Discontinuations due to AEs;
- Death.

Additional AEs may be considered for tabulation/summary based on recommendations from the TA MD and Pharmacovigilance and Patient Safety as deemed appropriate.

TEAEs will be summarized and presented by SOC and PTs using MedDRA. The SOC will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

TEAE will also be summarized by maximum severity and by maximum relationship.

The AEs of special interest (including but not limited to infection, opportunistic infection, herpes zoster, TB, gastrointestinal perforations, malignancies, MACE, renal dysfunction, anemia, increased CPK, and drug-related hepatic disorders) will be summarized.

All AEs leading to discontinuation of study drug will be presented in listing format. A listing by treatment group of TEAEs grouped by MedDRA SOC and PT with subject identification numbers will be generated.

8.1.5.2 Serious Adverse Events and Death

All treatment-emergent SAEs and AEs leading to death will also be presented in listing format. In addition, SAEs will be summarized by SOC and MedDRA PT.

8.1.5.3 Analysis of Laboratory and Vital Sign Data

Changes from baseline by visit; changes from baseline to minimum value, maximum value, and final values in continuous laboratory data; and vital signs will be summarized by treatment group.

Baseline values are defined as the last non-missing measurements recorded on or before the date of the first dose of study drug.

The laboratory data will be categorized as Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5 according to CTCAE criteria. The shift tables will tabulate the number and percentage of subjects with baseline and post-baseline values by grade levels.

Summary and listings will be provided for potentially clinically significant laboratory values and vital signs.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Individual upadacitinib plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods.

Data from this study may be combined with data from other studies for the population PK and exposure-response analyses. Population PK and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population PK and exposure-response analyses.

Population PK analyses will be performed using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling (NONMEM) approach with NONMEM software (Version 7, or a higher version). The CL/F and V/F of upadacitinib will be the PK parameters of major interest in the analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The relationship between the conditional estimates of CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using stepwise forward selection backward elimination approach. Relationships between upadacitinib plasma exposure and clinical observations will be explored.

Results of the PK and exposure-response analyses may be summarized in a separate report prior to regulatory filing of upadacitinib for the treatment of AS, rather than in the CSR. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The planned sample size of 170 for this study (with 1:1 randomization ratio) provides at least 90% power for a 26% difference in ASAS 40 response rate (assuming a placebo

ASAS 40 response rate of 20%). Power and sample size calculations are performed at two-sided significance level of 0.05 and accounting for a 10% dropout rate.

8.3 Randomization Methods

Subjects will be randomly assigned in a 1:1 ratio to one of the two treatment groups per study design diagram [Figure 1](#).

Randomization will be stratified by Screening hsCRP (\leq ULN vs. $>$ ULN) and geographic region (US/Canada, Japan, RoW). Subjects who were randomized to placebo at Baseline will receive upadacitinib 15 mg QD in an open-label manner at Week 14. See Section 5.5.3 for details.

9.0 Ethics

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

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

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

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly

provide written reports (e.g., ICH Expedited Reports and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject, and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding 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.

Low-dose CT scan of the whole spine will be performed only in subjects who voluntarily sign written consent to participate in the low-dose CT scan substudy and meet eligibility criteria. Written consent will be obtained as part of the main consent form, after the testing and potential risks have been explained and the subject has had an opportunity to

ask questions. If the subject does not consent to the low-dose CT scan substudy, it will not impact the subject's participation in the main study.

Samples for exploratory research/validation studies will only be collected if the subject has voluntarily signed and dated the separate written consent for exploratory research/validation studies, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent must be signed before the exploratory research/validation studies samples are collected and testing is performed. The separate written consent may be part of the main consent form. If the subject does not consent to the exploratory research/validation studies, it will not impact the subject's participation in the study.

In the event a subject withdraws from the main study, optional exploratory research/validation samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the Principal Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the Sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the Sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the Principal Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to

use in the study. The Investigator will provide the information without delay to each subject already participating in the study and will confirm the intention of each subject to continue the study or not. The Investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating 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 to the appropriate source document. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This AE data point required for eCRF completion can be entered directly in the eCRF.

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

eCRFs 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 eCRF 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.

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.

Subject- and site-reported data must be completed for each subject screened/enrolled in this study.

- The following data are being collected with an Electronic Patient-Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA:
 - Completed by Subject:
 - BASDAI
 - BASFI
 - PtGA

- Patient's Assessment of Total Back Pain
- Patient's Assessment of Nocturnal Back Pain
- Patient's Global Assessment of Pain
- AS QoL
- ASAS HI
- FACIT-F
- ISI
- WPAI
- Completed by Site:
 - Physician Global Assessment of Disease Activity

The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study-specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site Investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO 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 ePRO data. It will be possible for the Investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Tablet Based

- The instrument/scale will be collected electronically via a Tablet/Laptop device into which the subject will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by (ePRO Vendor). The Investigator and delegated staff will be able to access all uploaded subject-entered data via a password-protected website, up until the generation, receipt, and confirmation of the study archive.

11.0 Data Quality Assurance

Prior to the initiation of the study, a meeting will be held with AbbVie personnel, the investigators, and appropriate site personnel. This meeting will include a detailed discussion of the protocol, performance of study procedures, eCRF, subject dosing diary, and specimen collection methods.

The AbbVie monitor will monitor each site throughout the study. Source document review will be performed against entries on the eCRF, and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations.

All data hand entered in the database will be verified at AbbVie. Any discrepancies will be reviewed against the eCRF and corrected online. After completion of the entry process, computer logic and manual checks will be created by AbbVie to identify items such as inconsistent study dates. Any necessary corrections will be made by the site to the eCRF.

Routine hematology, serum chemistry and serology, and urinalysis, and other tests such as HBV/HCV testing, will be conducted using a central laboratory (refer to [Appendix E](#) and

Table 2). The data from these analyses will be electronically transferred from the central laboratory to the study database.

Laboratory tests including but not limited to urine pregnancy testing and ESR will be conducted locally by each study site (refer to [Appendix E](#) and [Table 2](#)). Sites will provide AbbVie with laboratory certifications and normal ranges for each local laboratory used. The full name, address, phone number and fax number for each local laboratory will also be included.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature, and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, 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 data from optional exploratory research may be provided to Investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

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 (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) 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 (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the Investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for upadacitinib.
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, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis

Protocol Date: 20 December 2019

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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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
		Therapeutic Area
		Therapeutic Area
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development
		Bioanalysis
		Medical Writing

Appendix C. 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.

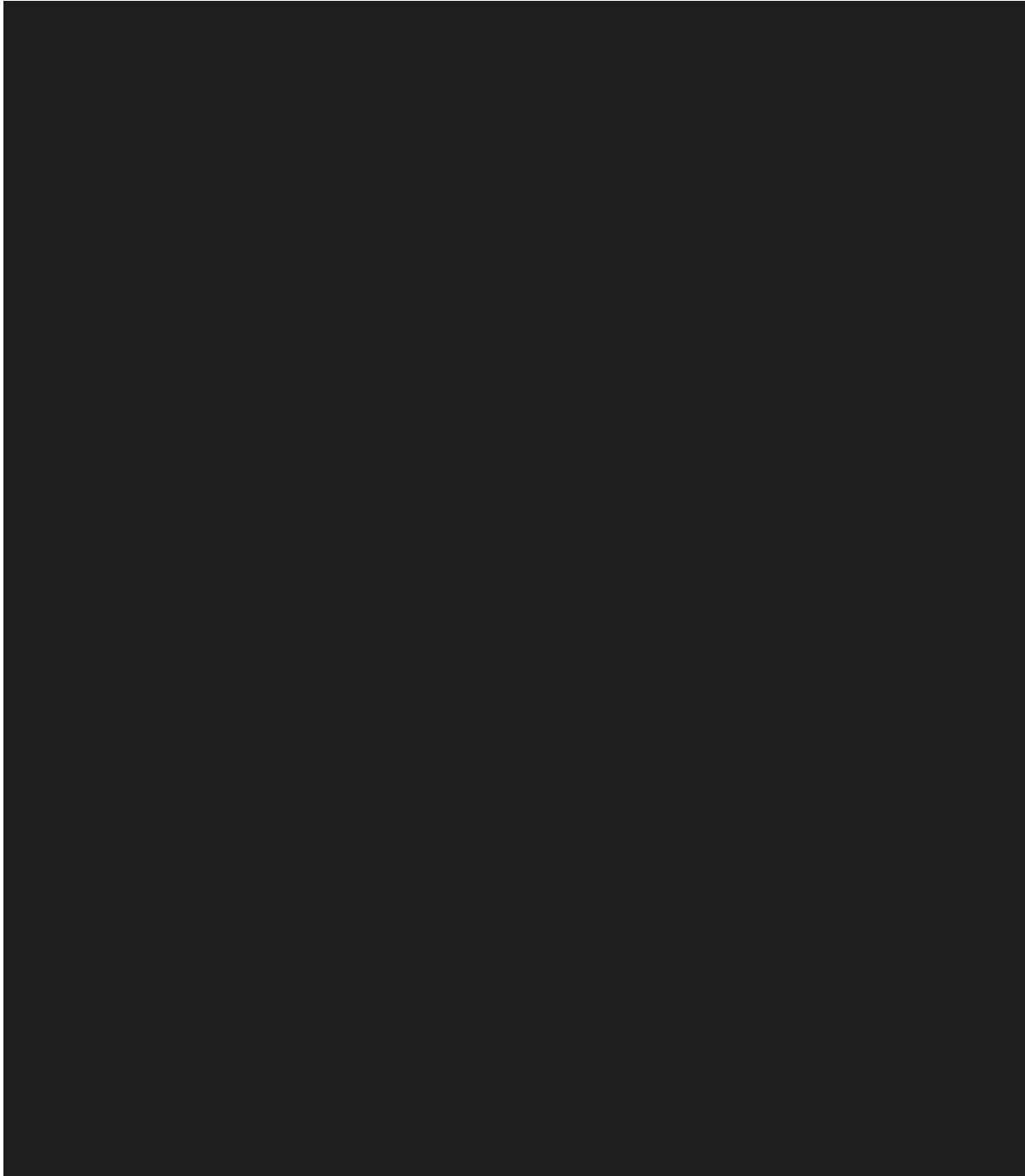
B. Grading

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:

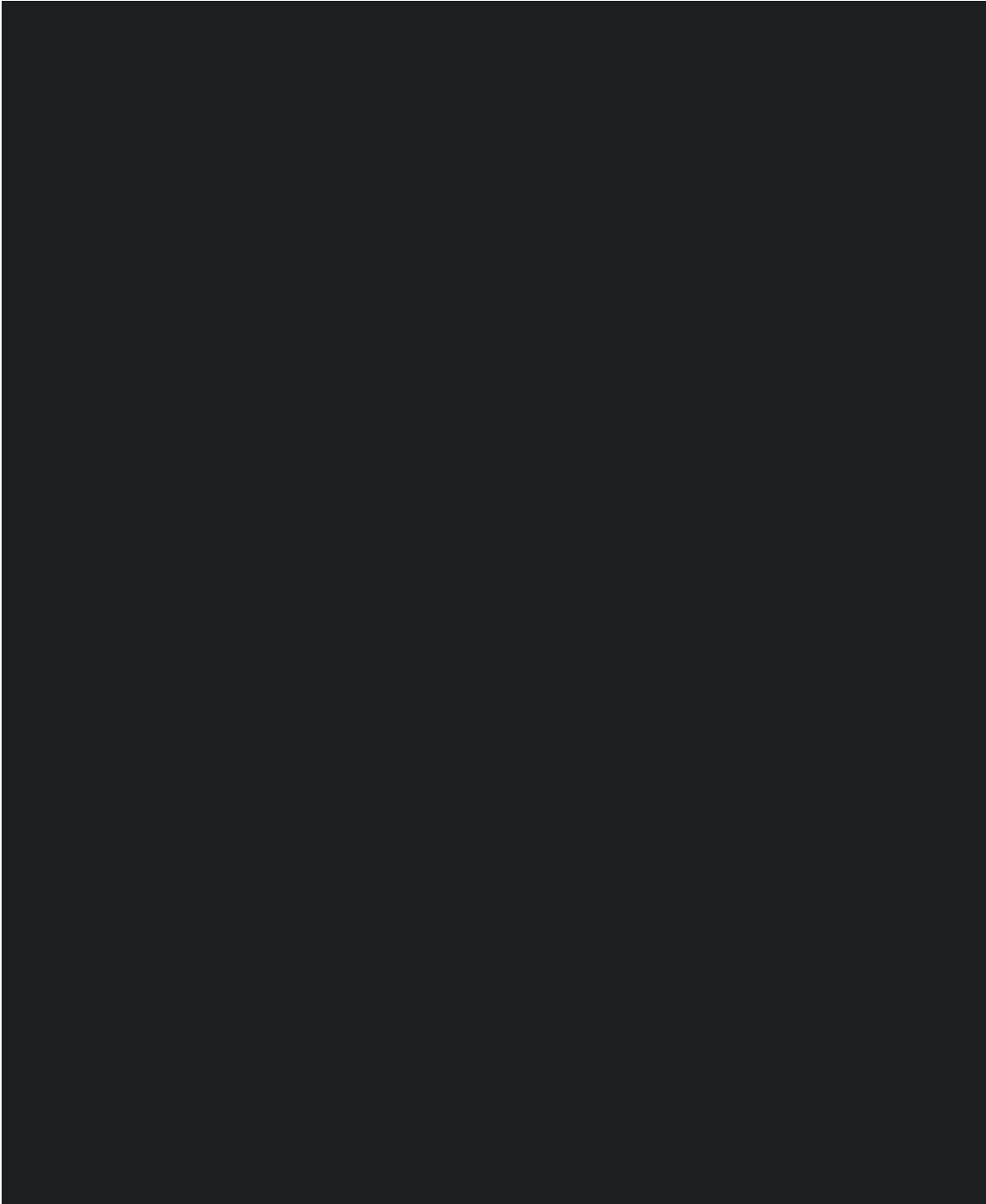
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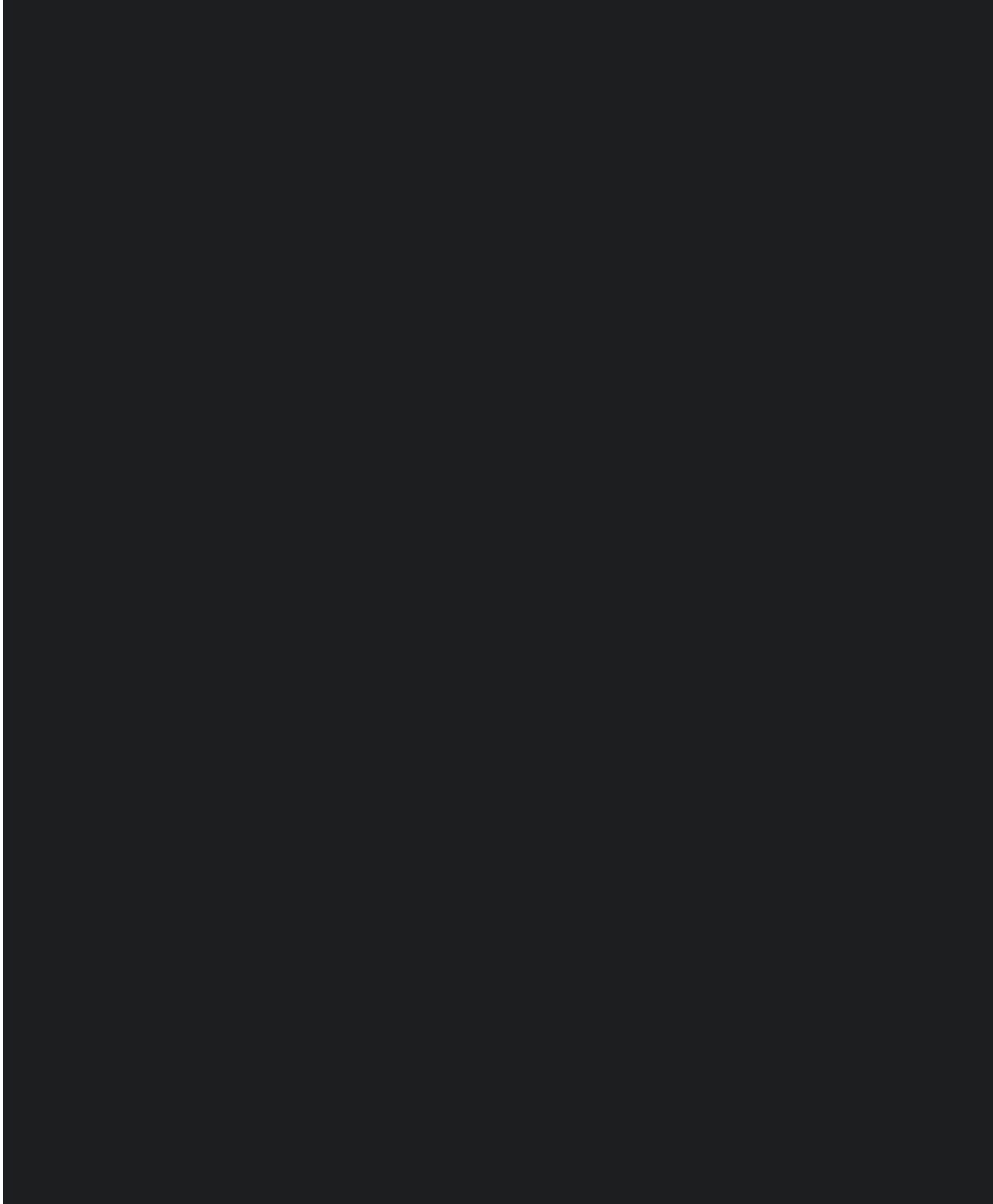
Appendix D. Local Requirements



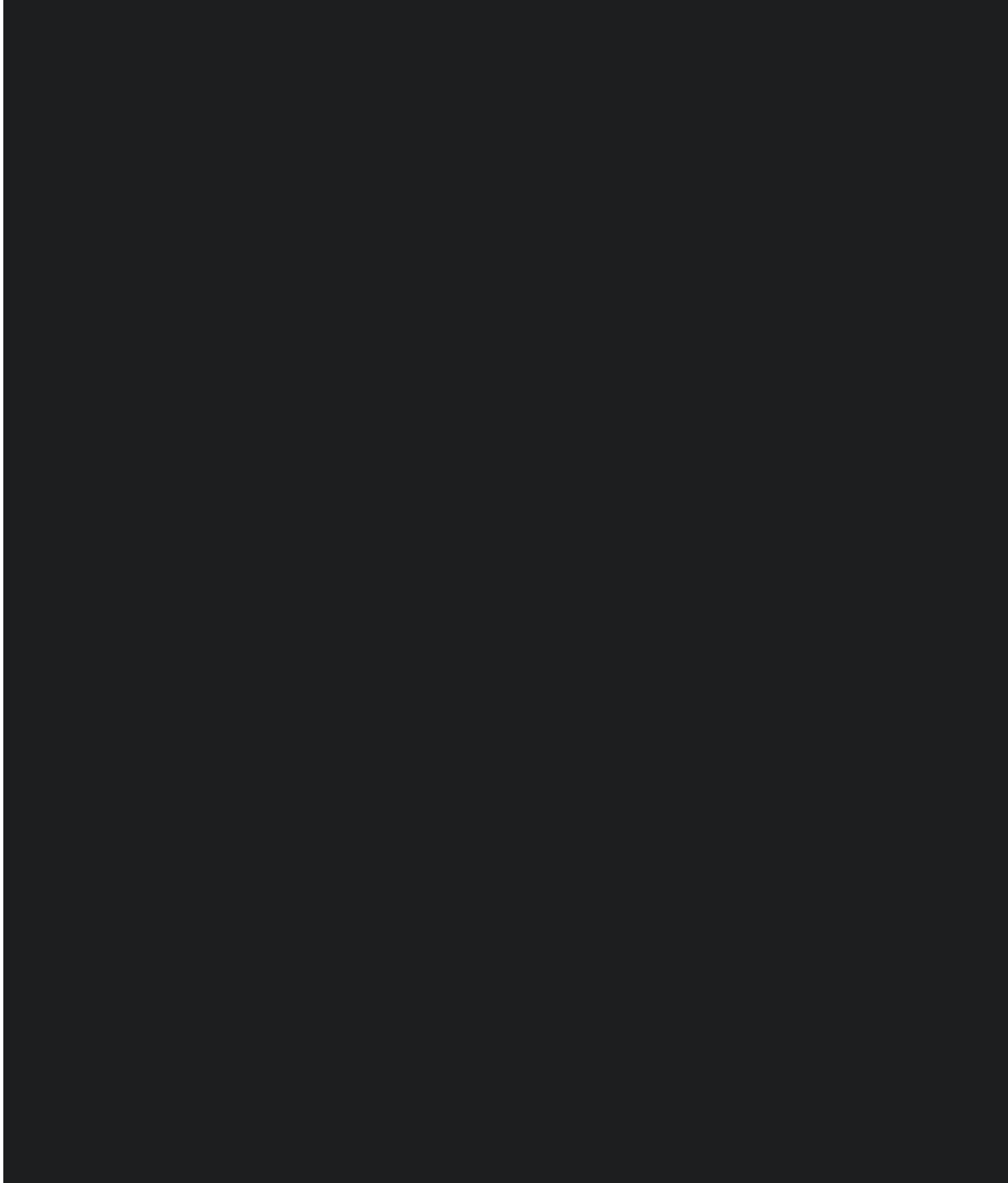












Appendix E. Study Activities

Activity	SCR (≤35D)	BL (D1)	Treatment Period																30 Day F/U Visit			
			Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 16 D113	Wk 20 D141	Wk 24 D169	Wk 32 D225	Wk 40 D281	Wk 52 D365	Wk 64 D449	Wk 76 D533	Wk 88 D617	Wk 96 D673	Wk 104 D729 /PD ^a				
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X ^b																				
Medical/Surgical History	X	X ^b																				
Alcohol and Nicotine Use	X							X								X					X	
Vital Signs/Weight/Height ^c	X ^c	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
Psoriasis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IBD		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																				
12-Lead ECG	X ^d																					X
Chest X-Ray	X ^d																					X ^e
AP Pelvis X-Ray ^f	X																					
Lateral Cervical-Spine and Lateral Lumbar-Spine X-Ray ^f	X																					X

Activity	SCR (≤ 35D)	BL (D1)	Treatment Period														30 Day F/U Visit		
			Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 16 D113	Wk 20 D141	Wk 24 D169	Wk 32 D225	Wk 40 D281	Wk 52 D365	Wk 64 D449	Wk 76 D533	Wk 88 D617		Wk 96 D673	Wk 104 D729 /PD ^a
MRI of Spine and SI Joints ^g		X				X												X	
Low-Dose CT Scan of Spine ^h		X																X	
Latent TB risk assessment form	X ^d																	X ^e	
TB Screening (QuantiFERON-TB Gold test and/or PPD Skin Test)	X ^d																	X ^e	
Pregnancy Test	X ⁱ	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j
Central lab tests Blood chemistry ^k Hematology Urinalysis ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte subsets		X						X										X	
ESR (local lab)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH ^m	X																		
HBV/HCV ⁿ	X						X ^o								X ^o	X ^o	X ^o	X ^o	X ^o
HIV ^p	X																		
HLA-B27 ^{q,r}		X																	
hsCRP ^s	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Activity	SCR (≤ 35D)	BL (D1)	Treatment Period															30 Day F/U Visit			
			Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 16 D113	Wk 20 D141	Wk 24 D169	Wk 32 D225	Wk 40 D281	Wk 52 D365	Wk 64 D449	Wk 76 D533	Wk 88 D617	Wk 96 D673		Wk 104 D729 /PD ^a		
<p>█ samples for exploratory research and validation studies (optional – see Appendix F)^t</p>			X ^u	X ^u	X ^v	X ^v	X ^v	X ^v													
Blood samples for upadacitinib PK assay			X	X	X	X	X	X						X ^v					X ^v		
Subject questionnaires ^w BASDAI Total Back Pain	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject questionnaires ^w BASFI PtGA Nocturnal Back Pain		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AS QoL ^w		X	X	X	X	X	X	X											X		
ASAS HI ^w		X	X	X	X	X	X	X											X		

Activity	BL (D1)	Treatment Period														30 Day F/U Visit			
		Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 16 D113	Wk 20 D141	Wk 24 D169	Wk 32 D225	Wk 40 D281	Wk 52 D365	Wk 64 D449	Wk 76 D533	Wk 88 D617		Wk 96 D673	Wk 104 D729 /PD ^a	
Subject questionnaires ^w FACIT – F ISI WPAI	X					X							X					X	
TJC/SJC	X					X							X					X	
Dactylitis	X					X							X					X	
BASMI _{lin}	X					X							X					X	
MASES	X			X		X							X					X	
PGA	X		X	X	X	X							X					X	
ASAS 20 calculation ^x										X			X					X	
Prior and Concomitant Therapy Assessment ^y	X	X	X	X	X	X				X			X					X	
Monitor AE ^z	X	X	X	X	X	X				X			X					X	
Randomization	X																		
Dispense Study Drug	X	X	X	X	X	X				X			X					X	
Subject Diary	X	X	X	X	X	X				X			X					X	

- AE = adverse event; AP = anterior-posterior; ASAS = Assessment of SpondyloArthritis international Society; AS QoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI_{lin} = Linear Bath Ankylosing Spondylitis Metrology Index; BL = Baseline Visit; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FSH = follicle-stimulating hormone; F/U = Follow-Up; HBV = hepatitis B virus; HCV = hepatitis C virus; HI = health index; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IBD = inflammatory bowel disease; IRT = Interactive Response Technology; ISI = Insomnia Severity Index; MASES = Maastricht AS enthesitis score; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PD = Premature Discontinuation; PGA = Physician's Global Disease Activity; PK = pharmacokinetics; PPD = purified protein derivative; PtGA = Patient's Global Assessment of Disease Activity; SCR = Screening; SI = sacroiliac; SIC = Swollen Joint Count; TB = tuberculosis; TJC = Tender Joint Count; Wk = Week; WPAI = Work Productivity and Activity Impairment
- a. Subjects who prematurely discontinue the study or study drug should complete the procedures outlined in the PD Visit within 2 weeks of last dose of study drug and preferably prior to the administration of new therapies.
 - b. Update Inclusion/Exclusion, prior and concomitant therapy, and Medical/Surgical History to prior to enrollment to assure subject eligibility.
 - c. Height will be measured at Screening Visit only.
 - d. These procedures will not be required if the subject had a previous normal ECG, normal CXR, or negative TB test within 90 days of Screening, provided all protocol-required documentation is available at the site and nothing has changed in the subjects health status since the time of the test that warrants a repeat test. Any documentation of past positive PPD or IGRA results may be acceptable; however, negative PPD or IGRA 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 have documented completion of a full course of TB prophylaxis prior to the Baseline Visit.
Refer to Section 5.3.1.1. Study Procedures, TB Testing for specific requirements for TB testing and TB prophylaxis.
 - e. Obtain chest x-ray for subjects with TB risk factors as identified by the TB risk assessment form for subjects living in areas endemic for TB or for subjects with a newly-positive QuantiferON-TB Gold test (and/or PPD skin test) after baseline. Refer to Section 5.3.1.1, Study Procedures, TB Testing for specific requirements for TB testing and TB Prophylaxis.
 - f. X-rays of the spine and pelvis will not be required during the Screening Period if the subject had a previous anteroposterior pelvis x-ray and lateral spine x rays within 90 days of the Screening Period, provided that the x-rays are confirmed to be adequate for the required evaluations and are deemed acceptable by the central imaging vendor.
 - g. MRI should be performed prior to or at Baseline in subjects who meet eligibility criteria, and at Week 14 and Week 104. If subject has a contraindication for MRI prior to enrollment, site must discuss with the AbbVie TA MD. If a site is unable to obtain the MRI prior to Baseline, a window of 3 days post-dose will be allowed.
 - h. Only for subjects at select sites who consent to participate in the low-dose CT scan substudy. Low-dose CT scan of the whole spine should be performed prior to or at the Baseline Visit in subjects who meet eligibility criteria, Week 52, and at Week 104. If a site is unable to obtain the low-dose CT of the whole spine prior to Baseline Visit, a window of 14 days post-dose will be allowed.

- i. For all women of childbearing potential, collect serum for pregnancy test only at Screening. If the serum pregnancy test is positive, the subject is considered a screen failure. If serum pregnancy test comes back borderline, a repeat test is necessary (pregnancy is an exclusion criterion). If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result, and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results. Refer to Section 5.3.1.1, Study Procedures, Pregnancy Test for additional details.
- j. For all women of childbearing potential, collect urine for pregnancy test at Baseline and all subsequent visits. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing, and perform a serum pregnancy test. Pregnant subjects must discontinue from study drug. Refer to Section 5.3.1.1, Study Procedures, Pregnancy Test for additional details.
- k. Minimum 8-hour fast. If a subject is not able to fast when necessary due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- l. A urine dipstick macroscopic 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 leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.
- m. FSH should be tested at Screening if the female subject is < 55 years of age AND has had no menses ≥ 12 months AND has no history of permanent surgical sterilization (defined in Section 5.2.4).
- n. In case of re-screening, there is no need to redraw HBV and HCV, provided the conditions noted in Section 5.3.1.1 are met and no more than 90 days have passed.
- o. For subjects in Japan only: Subjects with positive HBs Ab and/or positive HBc Ab results should have HBV-DNA PCR test performed at the specified visits; in cases where recurrence of HBV-DNA is observed, the subject should be discontinued from the study. This measure is not necessary in subjects with history of HBV vaccination and positive HBs Ab result.
- p. HIV testing will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health, and subject should receive or be referred for clinical care promptly. 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.
- q. In case of re-screening, there is no need to redraw HL-A-B27.
- r. Result does not need to be available to the site prior to enrollment.
- s. The hsCRP results starting after Baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, or the subject. Local laboratory or site testing for hsCRP or CRP is not allowed after Baseline. Results of tests such as hsCRP may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. As such, local hsCRP testing should not be performed until the last subject completes Period 1.
- t. Optional with signed ICF: if the ICF is not signed, samples for exploratory research or validation studies will not be collected. Refer to [Appendix F](#) for a description of the optional samples to be collected.

- u. Blood samples at Week 2 and Week 4 visits will be collected prior to dosing, and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample should be collected at any time during the visit.
- v. PK samples should be collected at any time during the visit. Subject should follow the regular dosing schedule.
- w. Prior to other procedures. Will be administered to the subject on an ePRO device.
- x. ASAS 20 criteria will be calculated by IRT.
- y. For subjects on concomitant NSAID therapy, the NSAID eCRF should be completed.
- z. SAEs will be collected starting from the time of signing informed consent; non-serious AEs will be collected starting from the first day of study drug dose. Any AE that occurs between Screening and Baseline Visit should be captured as medical history.
- aa. Subjects who were randomized to placebo at Baseline will receive upadacitinib 15 mg QD in an open-label manner at Week 14.

Appendix F. Optional Samples for Exploratory Research or Validation Studies

Activity	SCR (≤35D)	BL (D1)	Treatment Period														30 Day F/U Visit		
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 14	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88		Wk 96	Wk 104
			D15	D29	D57	D85	D99	D113	D141	D169	D225	D281	D365	D449	D533	D617	D673	D729	/PD



Appendix G. Latent TB Risk Assessment Form Example

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
 - Africa
 - Eastern Europe
 - Asia
 - Latin America
 - Caribbean Islands
 - Russia
3. Have you lived or worked in a prison, homeless shelter/refugee camp, immigration center, health care worker in a hospital or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
 - Chronic Cough
 - Chest pain, or pain with breathing or coughing
 - Blood-Streaked Sputum (coughing up blood)
 - Unexplained Weight Loss
 - Fever
 - Fatigue/Tiredness
 - Night Sweats
 - Shortness of Breath

From: <http://www.mayoclinic.org/diseases-conditions/tuberculosis/symptoms-causes/dxc-20188557>
http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix H. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.2 Synopsis

Subsection Methodology:

Sixth paragraph previously read:

Randomization will be stratified by baseline high sensitivity C-reactive protein (hsCRP) (\leq upper limit of normal [ULN] vs. $>$ ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

Has been changed to read:

Randomization will be stratified by Screening high sensitivity C-reactive protein (hsCRP) (\leq upper limit of normal [ULN] vs. $>$ ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

Section 3.2 Benefits and Risks

Sixth paragraph

Add: new last sentence

Events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib.

Section 5.1 Overall Study Design and Plan: Description

Seventh paragraph previously read:

Randomization will be stratified by baseline hsCRP (\leq ULN vs. $>$ ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

Has been changed to read:

Randomization will be stratified by Screening hsCRP (\leq ULN vs. $>$ ULN) and geographic region (United States [US]/Canada, Japan, Rest of the World [RoW]).

Section 5.2.3.2 Permitted Background AS Therapy

Fourth paragraph, third sentence previously read:

Once a joint is injected, it will be considered not evaluable/assessable ("NA") during the 28 days following injection.

Has been changed to read:

Once a joint is injected, it will be considered not evaluable/assessable ("NA") during the 90 days following injection.

Section 5.3.1.1 Study Procedures

Subsection TB Testing/TB Prophylaxis

Second paragraph, first sentence previously read:

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix G) and tested for TB infection by QuantiFERON-TB Gold test.

Has been changed to read:

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form ([Appendix G](#)) and tested for TB infection by QuantiFERON-TB Gold test (or IGRA equivalent).

Section 5.3.1.1 Study Procedures

Subsection TB Testing/TB Prophylaxis

Second paragraph, first bullet

Add: new second and third sentence

If a subject had a negative QuantiFERON-TB Gold (or IGRA equivalent) within 90 days prior to Screening and source documentation is available, the test does not need to be repeated provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TAMD.

Section 5.3.1.1 Study Procedures

Subsection TB Testing/TB Prophylaxis

Second paragraph, second bullet, first sentence previously read:

If a subject had a negative PPD Skin Test (also known as a TB Skin Test or Mantoux Test) within 90 days prior to Screening and a QuantiFERON-TB Gold test cannot be performed by Central Lab at Screening and source documentation is available, TB testing by PPD Skin Test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

Has been changed to read:

If a subject had a negative PPD Skin Test (also known as a TB Skin Test or Mantoux Test) within 90 days prior to Screening and a QuantiFERON-TB Gold test (or IGRA equivalent) cannot be performed by Central Lab at Screening and source documentation is available, TB testing by PPD Skin Test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

Section 5.4.1 Discontinuation of Individual Subjects

Second paragraph

Add: new last bullet

Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis.

Section 5.5.3 Method of Assigning Subjects to Treatment Groups

Fifth paragraph, first sentence previously read:

Randomization will be stratified by baseline hsCRP (\leq ULN vs. $>$ ULN) and geographic region (US/Canada, Japan, RoW).

Has been changed to read:

Randomization will be stratified by Screening hsCRP (\leq ULN vs. $>$ ULN) and geographic region (US/Canada, Japan, RoW).

Section 5.5.4 Selection and Timing of Dose for Each Subject

Last paragraph, last sentence previously read:

If the subject experiences a study drug interruption > 7 consecutive days during Weeks 1 through 14 (Period 1) or > 30 consecutive days after Week 14 (Period 2), they should notify the Investigator, and study drug should be discontinued.

Has been changed to read:

If the subject experiences a study drug interruption > 7 consecutive days during Weeks 1 through 14 (Period 1) or > 30 consecutive days during Period 2 they should notify the Investigator, and the Investigator will decide if study drug should be restarted.

Section 5.5.5.2 Blinding of Data for Data Monitoring Committee (DMC)

Add: new last paragraph

As of 18 April 2019, with all subjects having reached the end of Period 1, and after final review of unblinded safety data, the DMC concluded its oversight of this study.

Section 6.1.1.1 Adverse Event

Second paragraph, last sentence previously read:

Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

Has been changed to read:

Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study drug, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

Section 6.1.2 Adverse Event Severity

First paragraph previously read:

When criteria are available, events should be graded as described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).⁶⁰

Has been changed to read:

When criteria are available, events should be graded as described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.⁶⁰

Section 6.1.7 Toxicity Management

Third paragraph, sixth sentence previously read:

If study drug has been interrupted for a serious infection for more than 14 consecutive days during Period 1 of the study or 30 consecutive days thereafter, the subject must be discontinued from study drug.

Has been changed to read:

If study drug has been interrupted for a serious infection for more than 14 consecutive days during Period 1 of the study or 30 consecutive days thereafter, the subject must inform the Investigator and the Investigator can determine if study drug can be restarted.

Section 6.1.7 Toxicity Management

Add: new fourth paragraph

Herpes Zoster: If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

Section 6.1.7 Toxicity Management

Sixth paragraph

Add: new last sentence

Periodic skin examination is recommended for subjects who are at increased risk for skin cancer.

Section 6.1.7 Toxicity Management

Add: new seventh paragraph

Thrombosis Events: Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values Laboratory Parameter "Serum Creatinine"

First bullet, last sentence previously read:

If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to $\leq 1.5 \times$ baseline value and $> \text{ULN}$.

Has been changed to read:

If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to $\leq 1.5 \times$ baseline value and $\leq \text{ULN}$.

Section 6.1.7 Toxicity Management

Subsection Period 2

First bullet

Add: new last sentence

PI will make determination if study drug should be restarted for interruptions > 30 days.

Section 8.3 Randomization Methods

Last paragraph, first sentence previously read:

Randomization will be stratified by baseline hsCRP ($\leq \text{ULN}$ vs. $> \text{ULN}$) and geographic region (US/Canada, Japan, RoW).

Has been changed to read:

Randomization will be stratified by Screening hsCRP ($\leq \text{ULN}$ vs. $> \text{ULN}$) and geographic region (US/Canada, Japan, RoW).

Section 15.0 Reference List

Reference 27 and 60 previously read:


27. AbbVie. ABT-494 Investigator's Brochure Edition 6.1. 12 May 2016.
60. National Cancer Institute. CTCAE v. 4.0. Available from:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc.
Accessed on: 10 August 2017.

Has been changed to read:

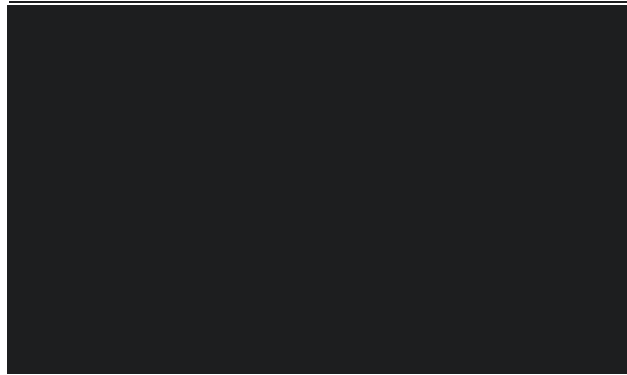
27. AbbVie. ABT-494 Investigator's Brochure Edition 10. 19 August 2019.
60. National Cancer Institute. CTCAE v. 4.03. Available from:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc.
Accessed on: 10 August 2017.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
		Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development
		Bioanalysis
		Medical Writing

Has been changed to read:

Name	Title	Functional Area
		Therapeutic Area
		Therapeutic Area
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development
		Bioanalysis
		Medical Writing

Appendix E. Study Activities

Table note "t."

Delete: last sentence

Sample collected at Screening will be for the stool sample only.