1.0 Title Page

Clinical Study Protocol M14-465

A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)

Incorporating Administrative Change 1, and Amendments 0.01, 0.01.01, 1, 2, 2.02, 3, 3.01, 4, 4.03, and 5

AbbVie Investigational Product:	Upadacitinib
Date:	01 December 2017
Development Phase:	3
Study Design:	A 48-week randomized, double-blind, parallel-group, active comparator-controlled period followed by a long-term extension period
EudraCT Number:	2015-003333-95
Investigators:	Multicenter trial (Investigator information is on file at AbbVie)
Sponsor:	AbbVie* 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Contact:	[redacted]

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

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.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	30 September 2015
Amendment 1	11 December 2015
Administrative Change 1	17 December 2015
Amendment 2	08 January 2016
Amendment 0.01 (Canada Only)	13 January 2016
Amendment 2.02 (Korea Only)	23 March 2016
Amendment 3	01 April 2016
Amendment 3.01 (Korea Only)	21 April 2016
Amendment 0.01.01 (Canada Only)	26 April 2016
Amendment 4	11 January 2017
Amendment 4.03 (Canada Only)	09 March 2017

The purpose of this amendment is to:

- Apply administrative changes throughout the protocol.

  Rationale: *Revised text to improve consistency and readability, and/or provide clarity.*
- Changed ABT-494 to Upadacitinib throughout the protocol

  Rationale: *Revised to reflect the recently approved International Nonproprietary Name.*
- Update Section 1.2, Synopsis

  Rationale: *Revised to be consistent with Amendment 5 revisions.*
- Update Section 1.3, List of Abbreviations

  Rationale: *Revised to be consistent with Amendment 5 revisions.*
- Update Section 5.1, Overall Study Design and Plan: Description

  Rationale:

  Revised to be consistent with Amendment 5 revisions.

Clarified that long term extension period is blinded until last subject completes Period 1.

Clarified that additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

Updated text to clarify TJC/SJC improvement requirements starting at Week 48 to remain on study drug.

Updated Figure 1 to align with protocol text.

Clarified that for subjects that discontinue study drug and continue on study, a second premature discontinuation visit is not required if the subject later withdraws from study.

Updated safety collection requirements for subjects that are treated with commercial adalimumab after end of study treatment.

Clarified the 30 day follow-up visit and 70 day follow-up call are not required for subjects who discontinued study drug and continued study participation with completion of at least one study visit approximately 30 days after last dose of oral or 70 days after last dose of subcutaneous study drug, respectively.

- Update Section 5.2.3.1, Permitted Background RA Therapy

  Rationale: *Updated csDMARD language to enable unbiased comparison of investigational product to active comparator up to end of Period 1.*

- Update Section 5.2.3.2, Prohibited Therapy

  Rationale:

  Updated text to align with permitted background corticosteroid requirements.

  Updated Table 1, Examples of Commonly Used Strong CYP3A Inhibitors and Inducers, to add Rifapentine.

  Updated herpes zoster vaccine language for subject safety prior to and after study drug.

  Updated to further explain the reason oral traditional Chinese medicines are not permitted.

- Update Section 5.2.4, Contraception Recommendations

Rationale: *Added clarification on requirements for contraception for females if child-bearing potential status changes during the course of the study.*

Updated required duration of contraception recommendations for males to reflect that upadacitinib is non-genotoxic, and showed no testicular findings in chronic animal toxicology studies, and had no impact on male or female fertility.

Added definition of surgical sterility for male subjects.

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

  Rationale:

  Updated Table 2 Study Activities (Period 1) to reflect Amendment 5 revisions.

  Updated Table 2 to clarify the frequency of the Latent TB Risk Assessment Form completion.

  Updated Table 2 to clarify that an annual ECG is required for all subjects.

  Updated foot note "s" to avoid introduction of bias by local CRP testing.

- Update Section 5.3.1.1, Study Procedures

  Rationale:

  Revised to include Rifapentine as excluded medication and added clarification on indeterminate QuantiFERON TB test results.

  Revised to prevent unnecessary initiation of TB prophylaxis in subject with indeterminate QuantiFERON-TB test results by allowing local testing.

  Revised to include Rifapentine as excluded medication for TB prophylaxis.

  Clarified annually is every 48 weeks to align with subject visit schedule.

  Updated to allow a pulmonologist to perform an assessment of the chest x-ray.

  Updated x-ray time points for subjects that prematurely discontinue from study drug but continue in the study to optimize x-ray assessments at Weeks 26, 48, and 96.

  Updated Figure 3 to align with protocol text.

  Updated to be consistent within the protocol that in the event post-baseline pregnancy test comes back borderline, a repeat test is required (≥ 3 days later) to document continued lack of a positive result.

Clarified requirements for recording lab abnormalities as AEs. Updated foot notes "i" and "k" to align with protocol text.

- Update Section 5.3.3, Efficacy Variables

  Rationale:

  Updated text to clarify efficacy variables.

  Updated text to provide clarity for ranked key secondary endpoints, other key secondary endpoints and additional endpoints.

- Update Section 5.4.1, Discontinuation of Individual Subjects

  Rationale:

  To clarify that starting at Week 48 at least 20% improvement in both swollen joint counts and tender joint counts compared to baseline is required to remain on study drug.

  To reduce redundancy and reference Section 5.1 where text is originally stated.

- Update Section 5.5.4, Selection and Timing of Dose for Each Subject

  Rationale: *Updated study drug interruption time frames to align with Section 6.1.7.*

- Update Section 5.5.5.1, Blinding

  Rationale: *Clarified who will remain blinded at study time points.*

- Update Section 6.1.1.3, Adverse Events of Special Interest

  Rationale: *Updated the adverse events of special interest that will be monitored during the study to align in content and presentation with the current version of the Product Safety Statistical Analysis Plan.*

  - *Serious infections, opportunistic infections, herpes zoster, and TB was separated into separate bullets for serious infections, opportunistic infections, herpes zoster and tuberculosis to indicate that these are separate adverse events of interest*
  - *Malignancy and lymphoproliferative disorders was reduced to Malignancy (all types) which encompasses all types of malignancy including lymphoproliferative malignancies*

- *Cardiovascular events was amended to adjudicated cardiovascular events as all cardiovascular events occurring in the RA Phase 3 development program will be adjudicated by an external cardiac adjudication committee (CAC)*
- *Removed hemoglobin effects as the term Anemia encompasses all hemoglobin effects of interest*
- *For consistency throughout the program updated terminology from Decreased neutrophil counts to the term Neutropenia*
- *For consistency throughout the program updated terminology from Decreased lymphocyte counts to the term Lymphopenia*
- *For consistency throughout the program updated terminology from Increased creatine phosphokinase (CPK) to Elevated creatine phosphokinase (CPK)*
- *Updated to include embolic and thrombotic events as adverse events of special interest, based on data reported for other JAK inhibitors*

- Update Section 6.1.3, Relationship to Study Drug

  Rationale: *Updated definition for assessing the relationship of adverse events to use of study drug per sponsor guidelines.*

- Update Section 6.1.4, Adverse Event Collection Period

  Rationale: *Implement Supplemental eCRF for thrombotic events.*

- Update Section 6.1.7, Toxicity Management and Table 7

  Rationale:

  Clarified gastrointestinal perforation to align with protocol text.

  Clarified that subject should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug.

  Clarified all abnormal lab tests that are considered clinically significant by the investigator should be followed to a satisfactory resolution.

  Updated text within Table 7 to improve readability and provide clarity. Added wording for management of subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening and laboratory values during study which may indicate active hepatitis.

Clarified toxicity management for ALT, AST, and INR.

Clarified toxicity management criteria for serum creatinine levels within normal reference range.

Clarified procedures for elevated CPK value (greater than or equal to 4 × ULN) but without any clinical signs and symptoms to allow continuation of treatment.

- Update 7.0, Protocol Deviations

  Rationale: *Updated AbbVie Clinical Contacts*

- Update Section 8.1, Statistical and Analytical Plans

  Rationale: *Clarified that additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.*

- Update Section 8.1.4.1.4, Multiplicity Control for the Primary and Ranked Key Secondary Endpoints

  Rationale: *Defined key secondary endpoints as ranked.*

- Update Section 8.1.4.1.5, Imputation Methods

  Rationale: *Updated text to clarify analysis details.*

- Update Section 8.1.5, Safety Analysis

  Rationale: *Updated text to clarify analysis details.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Updated list of Protocol Signatories responsible for Amendment 5.*

- Update Appendix C, Local Requirements

  Rationale: *Updated text for local country requirements for Canada to incorporate changes with Amendment 4.03 (Canada Only).*

- Update Appendix F, Latent TB Risk Assessment Form Example

  Rationale: *Revised to align with previous protocol example.*

- Update Appendix O, Rheumatology Common Toxicity Criteria v.2.0 Example

  Rationale: *Clarified that for CPK and serum creatinine NCI CTC grading will be used.*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix P.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-465
Name of Study Drug: Upadacitinib	**Phase of Development:** 3
Name of Active Ingredient: Upadacitinib	**Date of Protocol Synopsis:** 01 December 2017
Protocol Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)	
Objectives: **Period 1** 1. To compare the efficacy of upadacitinib 15 mg once daily (QD) versus placebo, and versus adalimumab (ADA) for the treatment of signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA who are on a stable background of methotrexate (MTX) and who have an inadequate response to MTX (MTX-IR). 2. To compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR). 3. To compare the safety and tolerability of upadacitinib 15 mg QD versus placebo, and versus ADA in subjects with moderately to severely active RA subjects who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR). **Period 2** To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	
Investigators: Multicenter	
Study Sites: Approximately 400	
Study Population: Adult female and male subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP) ≥ 5 mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week).	
Number of Subjects to be Enrolled: Approximately 1500	

Methodology:

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo and versus ADA for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of MTX and have an inadequate response to MTX (MTX-IR). Period 1 is also designed to compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

The study duration will include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes the last visit of the double-blind treatment period) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: Upadacitinib (ABT-494) 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg every other week [eow]) (N = 300)

Subjects will receive both oral study drug QD (either upadacitinib 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo) until the study is unblinded.

Subjects must have been on oral or parenteral MTX therapy for ≥ 3 months, on a stable MTX dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week), and must remain on a stable dose throughout the study; the MTX dose may be decreased only for safety reasons. In addition, all subjects should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Starting at the Week 26 visit (after Week 26 assessments have been performed), initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, is allowed as per local label. Starting at Week 48 (after Week 48 assessments have been performed) and thereafter, initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide).

Subjects with prior exposure to at most one biologic disease-modifying anti-rheumatic drug (bDMARD) (except ADA) for RA may be enrolled in the study (up to 20% of total number of subjects) after the required washout period is satisfied and if they have a) limited bDMARD exposure (< 3 months), OR b) response to a bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration). These subjects will be equally stratified across all treatment groups. Subjects who are considered bDMARD-inadequate responders (lack of efficacy), as determined by the Investigator, are not eligible.

Rescue therapy will be offered to subjects who meet the following criteria:

Methodology (Continued):

Placebo:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects will be switched to blinded upadacitinib treatment regardless of clinical response.

ADA:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded upadacitinib treatment.

Upadacitinib:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ADA treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ADA treatment.

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

Each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation. Subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14; in addition, subjects who prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint.

Subjects who complete the Week 48 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (up to 5 years). Subjects will continue study treatment as assigned in Period 1. Subjects who are assigned to the upadacitinib 15 mg QD treatment group at the end of Period 1 will continue to receive upadacitinib 15 mg QD in a blinded manner. Subjects who are assigned to adalimumab 40 mg eow at the end of Period 1 will continue to receive adalimumab 40 mg eow in a blinded manner. When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Each subject will undergo an x-ray examination of bilateral hands and feet at Week 96/Premature Discontinuation (unless repeat testing is needed due to failure to meet the quality requirements) and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous [redacted] weeks.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, at least 18 years old.
2. Diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 12.5 mg/week) for ≥ 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation.
4. Subject meets both of the following disease activity criteria:
   a. ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
   b. hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at Screening Visit.
5. Subject has at least one of the following at Screening:
   a. ≥ 3 bone erosions on x-ray; or
   b. ≥ 1 bone erosion and a positive rheumatoid factor; or
   c. ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody.
6. Subjects with prior exposure to only one bDMARD (except ADA) may be enrolled (up to 20% of total study population). Specifically, prior to enrollment:
   a. Patients with limited exposure to a bDMARD (< 3 months), OR
   b. Patients who are responding to a bDMARD but had to discontinue due to intolerability (regardless of treatment duration).
7. Except for MTX, subject must have discontinued all csDMARDs. The washout period for csDMARDs prior to the first dose of study is specified below or should be at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
   - ≥ 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).

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

Main Exclusion:

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Subjects who have had any exposure to adalimumab or subjects who have been treated with other bDMARD therapy for ≥ 3 months who are considered inadequate responders (lack of efficacy) to bDMARD therapy as determined by the Investigator.
3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms], or any arthritis with onset prior to age 17 years). History of secondary Sjogren's Syndrome is permitted.
4. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase > 2 × ULN; serum alanine transaminase > 2 × ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73m^2; total white blood cell count < 2,500/µL; absolute neutrophil count < 1,500/µL; platelet count < 100,000/µL; absolute lymphocyte count < 800/µL; and hemoglobin < 10 g/dL.

Investigational Product:	Upadacitinib
Dose:	15 mg QD
Mode of Administration:	Oral
Reference Therapy:	ADA, matching placebo for ADA, matching placebo for upadacitinib
Dose:	ADA 40 mg eow, matching placebo for upadacitinib QD, and matching placebo for ADA eow
Mode of Administration:	ADA and matching placebo for ADA will be administered by subcutaneous injection eow and upadacitinib and matching placebo will be given orally QD
Duration of Treatment:	Period 1: 48 weeks; Period 2: up to 5 years

Criteria for Evaluation:

Efficacy:

Period 1

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response at Week 12 (US/FDA regulatory purposes) or the proportion of subjects achieving clinical remission (CR) based on Disease Activity Score (DAS)28 (C-reactive protein [CRP]) at Week 12 (EU/EMA regulatory purposes).

ACR20 response rate will be determined based on 20% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain (Visual Analog Scale [VAS]), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI), or hsCRP.

CR is defined as DAS28 (CRP) < 2.6.

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

1. Change from baseline in Disease Activity Score (DAS)28 (C-reactive protein [CRP]) at Week 12;
2. Change from baseline in mTSS at Week 26;
3. Change from baseline in HAQ-DI at Week 12;
4. ACR50 response rate at Week 12 (non-inferiority of upadacitinib versus ADA);
5. Change from baseline in Short Form 36 (SF-36) Physical Component Score (PCS) at Week 12;
6. Proportion of subjects achieving low disease activity (LDA) based on DAS28 [CRP] ≤ 3.2 at Week 12;
7. Proportion of subjects achieving clinical remission (CR) based on DAS28 (CRP) at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12;
9. Change from baseline in morning stiffness at Week 12;
10. Change from baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) at Week 12;
11. ACR50 response rate at Week 12 (superiority of upadacitinib vs. ADA);
12. Change from baseline in Patient's Assessment of Pain at Week 12 (superiority of upadacitinib vs. ADA);
13. Change from baseline in HAQ-DI at Week 12 (superiority of upadacitinib vs. ADA).

Criteria for Evaluation (Continued):

Efficacy (Continued):

Other key secondary endpoints (upadacitinib versus placebo) for US/FDA regulatory purposes are:

- ACR50 response rate at Week 12
- ACR70 response rate at Week 12
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

1. The change from baseline in modified Total Sharp Score (mTSS) at Week 26;
2. Proportion of subjects achieving LDA based on DAS28 [CRP] ≤ 3.2 at Week 12;
3. Change from baseline in DAS28 (CRP) at Week 12;
4. Change from baseline in HAQ-DI at Week 12;
5. ACR20 response rate at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of upadacitinib versus ADA);
7. Change from baseline in SF-36 PCS at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12
9. Change from baseline in morning stiffness at Week 12.
10. Change from baseline in FACIT-F at Week 12
11. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26;

Other key secondary endpoints (upadacitinib versus placebo) for EU/EMA regulatory purposes are:

1. ACR50 response rate at Week 12
2. ACR70 response rate at Week 12

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional endpoints (upadacitinib versus placebo and adalimumab) are:

- Change from baseline in individual components of ACR response at all visits;
- ACR20/50/70 response rates at all visits;
- Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]) at all visits;
- Change from baseline in CDAI and SDAI at all visits;
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP) and DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria at all visits (see below);
- Change from baseline in morning stiffness at all visits;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22 at all visits;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 at all visits;
- ACR/EULAR Boolean remission at all visits;
- Change from baseline in EQ-5D-5L, SF-36, FACIT-F and RA-WIS at Weeks 12, 26, and 48;
- Change from baseline in modified Total Sharp Score (mTSS) at Weeks 26 and 48;
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Weeks 26 and 48;
- Change from baseline in joint space narrowing score and joint erosion score at Weeks 26 and 48

Criteria for Evaluation (Continued):

Efficacy (Continued):

	DAS28 (CRP) and DAS28 (ESR)	SDAI	CDAI
LDA	≤ 3.2	≤ 11.0	≤ 10
CR	< 2.6	≤ 3.3	≤ 2.8

Period 2

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 60, 72, 84, 96, and every 12 weeks thereafter until completion of the study:

- ACR20/50/70 response rates;
- Change from baseline in individual ACR components;
- Change from baseline in DAS28 (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in CDAI and SDAI;
- Change from baseline in morning stiffness;
- Proportion of subjects achieving LDA and the proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria (as defined for Period 1);
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.22;
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3;
- Concomitant corticosteroid use (systemic use and intra-articular injections);
- ACR/EULAR Boolean remission.

Additionally, assessment for the evaluation of radiographic changes in Period 2 will occur at Week 96 and every 96 weeks thereafter (or Premature Discontinuation visit):

- Change from baseline in modified Total Sharp Score (mTSS);
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS of ≤ 0);
- Change from baseline in Radiographic joint space narrowing and erosion scores.

Pharmacokinetic (Period 1 Only):

Blood samples for assay of upadacitinib and possibly other medications in plasma will be collected at Weeks 2, 4, 8, 12, 14, 18, 22, 26, 30, 36, 42, and 48/Premature Discontinuation.

Exploratory Research Variables and Validation Studies (Optional) (Period 1 Only):

Prognostic, predictive, and pharmacodynamics biomarkers signatures may be evaluated. Samples for pharmacogenetic, epigenetic, transcriptomic, and proteomic and targeted protein investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites, or lipids.

Safety:

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

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.

Period 1 Efficacy

Analysis of the Primary and Key Secondary Endpoints:

All statistical comparisons of upadacitinib versus comparators for the primary and key secondary endpoints will be conducted using a two-sided alpha = 0.05 level of significance.

In order to preserve Type I error, a step-down approach will be used to test the primary and ranked key secondary endpoints where statistical significance can be claimed for a lower ranked endpoint only if the previous endpoints in the sequence meets the requirements of significance.

For binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparisons between upadacitinib and placebo will be conducted using the Cochran-Mantel-Haenszel test adjusting for main stratification factors. For LDA response rates at Week 12, analysis will be conducted to test the non-inferiority of upadacitinib versus ADA using the 95% confidence interval of treatment difference against a non-inferiority margin of 10%. For ACR50 response rate at Week 12, similar analysis of non-inferiority will be conducted for US/FDA purposes. Superiority of upadacitinib vs ADA will also be tested for LDA and ACR50.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between upadacitinib and placebo will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates. For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of upadacitinib vs adalimumab will also be tested.

For mTSS-based endpoints, both linear extrapolation and As Observed (AO) analyses will be conducted. For all other endpoints, non-responder imputation approach will serve as the primary analysis approach for key binary endpoints and multiple imputation will serve as the primary analysis approach for key continuous endpoints. Sensitivity analyses based on observed cases approach will also be conducted for key endpoints.

Long-Term Efficacy for Period 1 and Period 2 Combined

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

Pharmacokinetic:

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.

Statistical Methods (Continued):

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. Analyses will be conducted for both short term and long term. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from baseline to defined time points will be tabulated.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-CCP	anti-cyclic citrullinated peptide
AST	aspartate transaminase
AUC	Area under the plasma concentration-time curve
BCG	Bacille Calmette-Guérin
bDMARD	biologic disease-modifying anti-rheumatic drug
BID	twice daily (Latin: bis in die)
BUN	blood urea nitrogen
CBC	complete blood count
CDAI	clinical disease activity index
CL/F	apparent clearance
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
CPK	creatine phosphokinase
CR	clinical remission
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CSR	clinical study report
CXR	chest x-ray
CYP	cytochrome
DAS	disease activity score
DMARD	disease-modifying anti-rheumatic drug
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
eow	every other week
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL-5D-5L
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
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBc Ab/anti-HBc	Hepatitis B core antibody
HBs Ab/anti-HBs	Hepatitis B surface antibody
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
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
IAG	Imaging Acquisition Guidelines
ICH	International Conference On Harmonization
IEC	independent ethics committee
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
INR	international normalized ratio
IR	inadequate response
IRB	institutional review board
IRT	interactive response technology
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
MCID	minimum clinically important differences
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mTSS	modified Total Sharp Score
MTX	methotrexate
MTX-IR	methotrexate inadequate responder
NA	no assessment
NMSC	non-melanoma skin cancer
NONMEM	non-linear mixed-effects modeling
NRI	non-responder imputation
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
OC	observed cases
OLE	open-label extension
PCR	polymerase chain reaction
PCS	physical component score
PD	premature discontinuation
PhGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic
PPD	purified protein derivative
PRN	as needed (Latin: pro re nata)
PRO	patient-reported outcome
PT	preferred term
PtGA	Patient's Global Assessment of Disease Activity
QD	once daily (Latin: quaque die)
RA	rheumatoid arthritis
RA-WIS	Work Instability Scale for Rheumatoid Arthritis
RAVE®	EDC system from Medidata
RBC	red blood cell
RCT	randomized controlled trial
RF	rheumatoid factor

RNA	Ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SDAI	simplified disease activity index
SF-36	Short Form-36
SJC	swollen joint count
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T2T	treat-to-target
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
TNF-IR	tumor necrosis factor inadequate responder
Tyk2	Tyrosine kinase 2
ULN	upper limit of normal
V/F	apparent volume of distribution
VAS	visual analog scale
WBC	white blood cell

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology. The hallmark feature of RA is an inflammatory process manifested by persistent symmetric polyarthritis of synovial joints which can ultimately lead to bone erosions, deformity, and disability. Left untreated, or inadequately treated, progressive functional impairment with increasing disability occurs leading to a reduction in quality of life. The prevalence of RA in the general population is approximately 1%, and increases with age in both genders, with women being more prone to developing RA than men. Early therapy with disease-modifying anti-rheumatic drugs (DMARDs) is the standard of care, including conventional synthetic DMARDs (csDMARDs) (e.g., methotrexate [MTX], sulfasalazine, hydroxychloroquine, and leflunomide), and biologic DMARDs (bDMARDs) (e.g., anti-tumor necrosis factor [TNF] and non-anti-TNF biologics).

The European League Against Rheumatism (EULAR) recommends a Treat-to-Target (T2T) approach to initiate therapy immediately after diagnosis of RA with a goal of achieving clinical remission (CR) or low disease activity (LDA), as these are associated with improved long-term outcomes.[1-3] Also, in line with recent advances in early diagnosis, new classification criteria have been developed. The 2010 American College of Rheumatology (ACR)/EULAR classification criteria redefined the paradigm of RA by focusing on features at earlier stages of disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features.[4]

Despite major progress in the treatment of RA, there still remains a large unmet medical need, as only a small percentage of RA patients reach or maintain a status of LDA or CR over time or need to discontinue due to safety or tolerability issues.[5,6] Novel therapies are therefore needed to complement the available interventions to address the unmet need.[5-7]

JAK Inhibitor

Evidence suggests that inhibition of Janus kinase (JAK)-mediated pathways is a promising approach for the treatment of patients with this chronic disease.[8] AbbVie is developing a small molecule inhibitor of JAK, upadacitinib (ABT-494), 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.[9] 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 which have demonstrated efficacy in individuals with RA.[10-14] Tofacitinib, the first in this class, has been approved in the United States 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.[8] Upadacitinib is a novel selective JAK1 inhibitor being developed for the treatment of adult patients with moderately to severely active RA. In an in vitro setting, upadacitinib potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit-risk profile in patients with RA. The clinical hypothesis is that upadacitinib should be effective in decreasing joint

inflammation and damage associated with RA by interfering with JAK1-mediated signaling pathways (i.e., interleukin-6) without causing excessive anemia due to its reduced activity against JAK2 (IC_{50} 120 nM), which is essential for erythropoietin signaling. Upadacitinib is also less potent against JAK3 (IC_{50} 2.3 μM), 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 a pan JAK inhibitor or less selective JAK inhibitors.

Phase 2 Studies with Upadacitinib

The Phase 2 program for upadacitinib consisted of 2 randomized controlled trials (RCTs), both on stable background MTX therapy, in subjects with moderately to severely active RA and one open-label extension (OLE) study (Study M13-538; NCT02049138) for those subjects who had completed either one of the RCTs. Study M13-550 (NCT01960855) enrolled subjects who had an inadequate response to anti-TNF therapy and Study M13-537 (NCT02066389) enrolled subjects who had shown an inadequate response to MTX. A total of 4 twice daily (BID) and 1 once daily (QD) dose regimens of upadacitinib immediate release capsules (3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID, and 24 mg QD) were evaluated.

In TNF-inadequate responder (TNF-IR) subjects, who represent the population with the greatest unmet need, the primary endpoint of ACR20 response rate at Week 12 was significantly greater at all doses of upadacitinib (up to 73%) compared with placebo (35%). In addition, numerically higher proportions of subjects achieved ACR50 and ACR70 responses and LDA (based on Disease Activity Score [DAS]28 C-Reactive Protein [CRP] and Clinical Disease Activity Index [CDAI]) in the upadacitinib dose groups versus placebo.

In MTX-inadequate responder (MTX-IR) subjects, the primary endpoint of ACR20 response rate at Week 12 was significantly greater (up to 82%) at all but the lowest dose

of upadacitinib compared with placebo (50%). At all doses of upadacitinib compared to placebo, significantly higher proportions of subjects achieved LDA and CR at Week 12.

Safety data from these two 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 (≥ 5%) AEs 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 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. 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]). Among subjects with laboratory evidence of systemic inflammation (as evidenced by high-sensitivity C-reactive protein [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.

3.1 Differences Statement

Study M14-465 differs from other upadacitinib studies as it is the first study to evaluate the safety and efficacy (both clinical and structural) of upadacitinib in the MTX-IR population, and to use adalimumab (ADA) as an active comparator.

3.2 Benefits and Risks

Despite the availability of various RA therapies, including csDMARDs and bDMARDs, many patients still do not respond adequately to these treatments, or gradually lose response over time. Upadacitinib is a novel selective JAK1 inhibitor with the ability to decrease joint inflammation and damage mediated by JAK1 signaling while having minimal inhibitory effects on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways. The Phase 2 program with upadacitinib 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.[13-21] Taken together, the safety and efficacy data from the Phase 2 program support further development of upadacitinib in Phase 3 in subjects with RA.

4.0 Study Objectives

Period 1

1. To compare the efficacy of upadacitinib 15 mg QD versus placebo, and versus ADA for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR).
2. To compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR).
3. To compare the safety and tolerability of upadacitinib 15 mg QD versus placebo, and versus ADA in subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR).

Period 2

To evaluate the long-term safety, tolerability and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo and versus ADA for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of MTX and have an inadequate response to MTX (MTX-IR). Period 1 is also designed to compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

The study is designed to enroll approximately 1500 subjects at approximately 510 study centers worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The study duration will include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes Period 1) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: Upadacitinib (ABT-494) 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg every other week [eow]) (N = 300)

Subjects will receive both oral study drug QD (either upadacitinib 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo) until the study is unblinded.

Subjects must have been on oral or parenteral MTX therapy for ≥ 3 months, on a stable MTX dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week), and must remain on a stable dose throughout the study; the MTX dose may be decreased only for safety reasons. In addition, all subjects should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Starting at the Week 26 visit (after Week 26 assessments have been performed) and thereafter, initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol is allowed as per local label. Starting at Week 48 (after Week 48 assessments have been performed) and thereafter, initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide).

Starting at the Week 48 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) (see Section 5.4.1) must be discontinued from study drug.

Subjects with prior exposure to at most one biologic disease-modifying anti-rheumatic drug (bDMARD) (except ADA) for RA may be enrolled in the study (up to 20% of total number of subjects) after the required washout period is satisfied and if they have

a) limited bDMARD exposure (< 3 months), OR b) response to a bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration) (for washout periods, see Inclusion Criterion 8, Section 5.2.1). These subjects will be equally stratified across all treatment groups. Subjects who are considered bDMARD-inadequate responders, as determined by the Investigator, are not eligible.

Rescue therapy will be offered to subjects as described in Section 5.2.3.3 (rescue therapy).

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

Each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation. Subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14; in addition, subjects who prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint (refer to Section 5.3.1.1 for additional details).

Joint x-rays will be sent to the central imaging vendor designated by the Sponsor. The x-rays will only be assessed by the imaging vendor for erosions and joint space narrowing, and will not be assessed for any other clinically significant findings that may impact a subject's health.

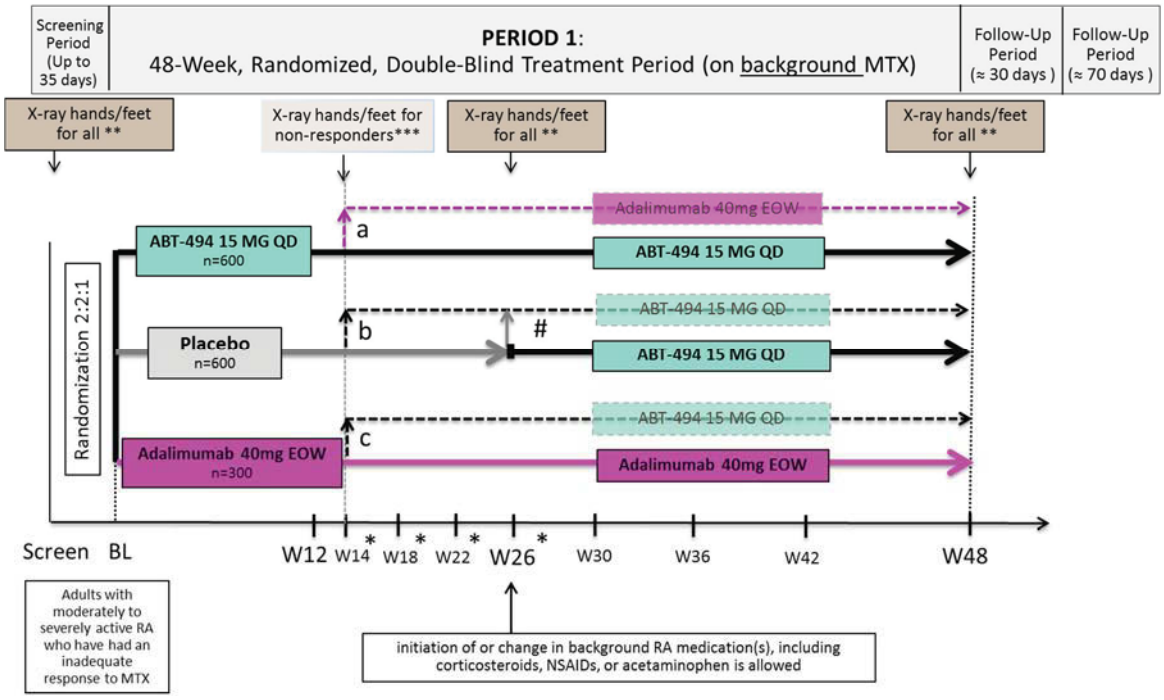
Subjects who complete the Week 48 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (up to 5 years). Subjects will continue study treatment as assigned in Period 1. Subjects who are assigned to the upadacitinib 15 mg

QD treatment group at the end of Period 1 will continue to receive upadacitinib 15 mg QD in a blinded manner. Subjects who are assigned to adalimumab 40 mg eow at the end of Period 1 will continue to receive adalimumab 40 mg eow in a blinded manner. When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Each subject will undergo an x-ray examination of bilateral hands and feet at Week 96/Premature Discontinuation (unless repeat testing is needed due to failure to meet the quality requirements) and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous [redacted] weeks.

Schematics of Period 1 and Period 2 are shown in Figure 1 and Figure 2, respectively.

Figure 1. Period 1 Study Design



BL = baseline; EOW = every other week; MTX = methotrexate; QD = once daily; RA = rheumatoid arthritis; SJC = swollen joint count; TJC = tender joint count; W = week

\# At W26, all placebo patients will be switched to upadacitinib 15 mg regardless of response.

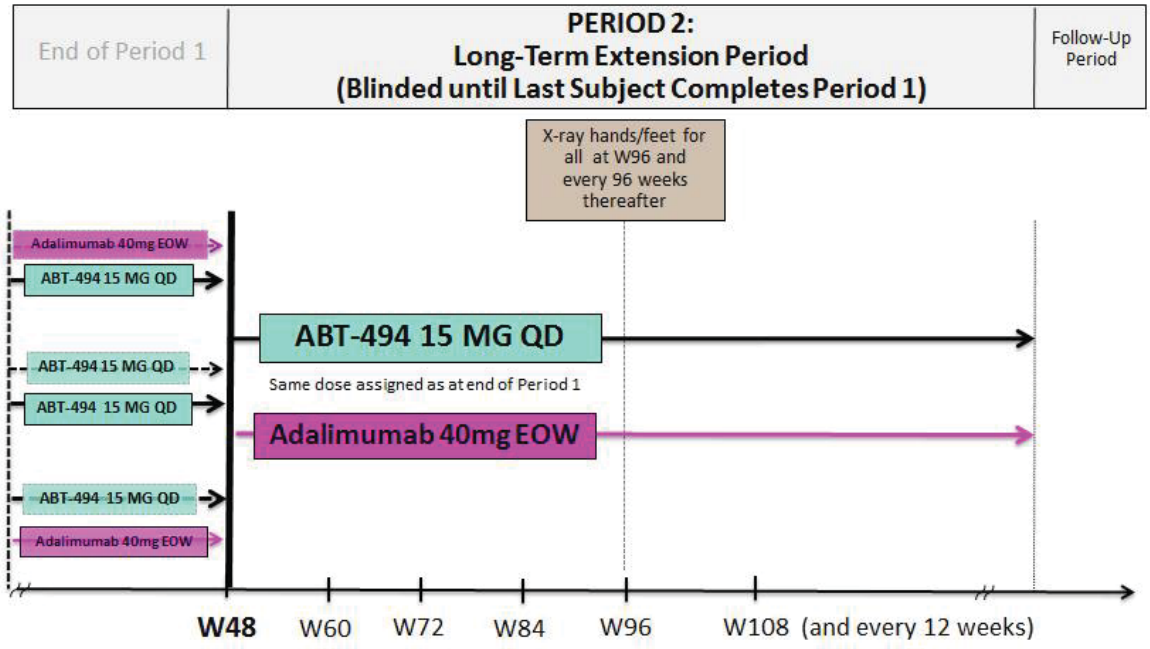
** All patients will receive x-rays of hands and feet at Screening, W26, and W48.

*** X-rays at W14 will only be performed for non-responders, see Section 5.3.1.1.

Notes: The follow-up period is only for subjects who do not enter Period 2.

Early escape for non-responders: (a) from upadacitinib 15 mg QD to adalimumab at W14, W18, W22, or W26; (b) from placebo to upadacitinib 15 mg QD at W14, W18, or W22; (c) from adalimumab to upadacitinib 15 mg QD at W14, W18, W22, or W26. Non-response at W14, W18, or W22 is defined as not achieving ≥ 20% improvement in TJC and SJC compared to baseline. Non-response at W26 is defined as not achieving LDA according to CDAI (LDA defined as CDAI ≤ 10). For more details regarding x-rays of hands and feet, see Section 5.3.1.1.

Figure 2. Period 2 Study Design



csDMARD = conventional synthetic disease modifying anti-rheumatic drug; EOW = every other week; NSAIDs = non-steroidal anti-inflammatory drugs; QD = once daily; RA = rheumatoid arthritis; W = week

Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Table 2. 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 with no additional re-screening possible. Redrawing samples if initial samples were unable to be analyzed would not count as a retest since 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 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 assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) and/or a purified protein derivative (PPD) test (or equivalent) (or both if required per local guidelines), chest x-ray and electrocardiogram (ECG), 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.

Period 1 (48-Week Randomized, Double-Blind Treatment Period)

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 48 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, 14, 18, 22, 26, 30, 36, 42, and 48. A ± 3 day window is permitted around scheduled study visits until Week 30 and ± 7 days for the remainder of the period. The last dose of oral study drug in Period 1 is taken the day prior to the Week 48 visit. Subjects who complete Period 1, but decide not to continue in Period 2 should complete a 30 day follow-up visit after the last dose of study drug.

Period 2 (Long-Term Extension Period [up to 5 years])

Period 2 will begin at the Week 48 visit after all assessments have been completed. During Period 2, subjects will have a study visit at Weeks 60, 72, 84, 96, and every 12 weeks thereafter until completion of the study. A ± 7 day window is permitted around scheduled study visits. Starting at Week 48 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone

who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) (see Section 5.4.1) must be discontinued from study drug.

Discontinuation of Study Drug and Continuation of Study Participation (Period 1 and Period 2)

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 Visit (PD visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Table 2 and Table 4, and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood sample collection for optional exploratory research and validation studies. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply; this includes 20% TJC/SJC calculations at Weeks 14 – 22, and Week 48 and thereafter, as well as CDAI calculation at Week 26, if applicable. 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) (Period 1 and Period 2)

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 Premature Discontinuation visit (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) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. For subjects on subcutaneous study drug, if the subject is willing, a 70-day follow-up phone call may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

Follow-Up Period

Subjects who have completed the last visit of Period 1 (Week 48) but decided not to participate in the extension Period 2 will have a follow-up visit approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AEs and to collect vital signs and clinical laboratory tests.

A 30-day follow-up visit will also occur for subjects who have completed Period 2.

A follow-up phone call will also occur 70 days after the last administration of subcutaneous study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

The 30 day follow-up visit and 70 day follow-up call are not required for subjects who discontinued study drug and continued study participation with completion of at least one study visit approximately 30 days after last dose of oral or 70 days after last dose of subcutaneous study drug, respectively.

5.2 Selection of Study Population

It is anticipated that approximately 1500 subjects with moderately to severely active RA will be randomized at approximately 510 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. Adult male or female, at least 18 years old.
2. Diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/EULAR classification criteria for RA.

3. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 12.5 mg/week) for ≥ 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation.
   - Additional local requirements may apply. Refer to Appendix C for local requirements (Hong Kong, Korea, Malaysia, Singapore and Taiwan).
4. Subject meets both of the following disease activity criteria:
   a. ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
   b. hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at Screening Visit.
5. Subject has at least one of the following at Screening:
   - ≥ 3 bone erosions on x-ray; or
   c. ≥ 1 bone erosion and a positive rheumatoid factor (RF); or
   d. ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide (anti-CCP) autoantibody.
6. Stable dose of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen/paracetamol must have been at a stable dose ≥ 1 week prior to the first dose of study drug; oral corticosteroids (equivalent to prednisone ≤ 10 mg/day) or inhaled corticosteroids for stable medical conditions are allowed but must have been at a stable dose ≥ 4 weeks prior to the first dose of study drug.
7. Subjects with prior exposure to at most one bDMARD (except ADA) may be enrolled (up to 20% of total study population). Specifically, prior to enrollment:
   a. Patients with limited exposure to a bDMARD (< 3 months), OR
   b. Patients who are responding to a bDMARD but had to discontinue due to intolerability (regardless of treatment duration).

8. Subjects must have discontinued bDMARD therapy prior to the first dose of study drug. The washout period for bDMARDs prior to the first dose of study drug is specified below or at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks for etanercept;
   - ≥ 8 weeks for infliximab, certolizumab, golimumab, abatacept, and tocilizumab;
   - ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pre-treatment level or normal reference range (central lab) if pre-treatment levels are not available.
9. Except for MTX, subject must have discontinued all csDMARDs. The washout period for csDMARDs prior to the first dose of study is specified below or should be at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;*
   - ≥ 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).

     * Additional local requirements may apply. Refer to Appendix C for local requirements (Korea.)
10. Subjects must have discontinued all high-potency opiates at least 1 week and oral traditional Chinese medicine for at least 4 weeks prior to the first dose of study drug (refer to Section 5.2.3.2 for prohibited medications).
11. 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.

12. 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 150 days after the last dose of subcutaneous study drug and 30 days after the last dose of oral study drug.
    - Additional local requirements may apply. Refer to Appendix C for local requirements (Canada and Korea.)
13. 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 C for local requirements (Canada and Korea.)
14. 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.

Rationale for Inclusion Criteria

1 – 10	To select the appropriate subject population
11 – 13	The effect of upadacitinib on pregnancy and reproduction is unknown
14	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

1. Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Subjects who have had any exposure to adalimumab or subjects who have been treated with other bDMARD therapy for ≥ 3 months who are considered inadequate

responders (lack of efficacy) to bDMARD therapy as determined by the Investigator.

3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms], or any arthritis with onset prior to age 17 years). History of secondary Sjogren's Syndrome is permitted.
4. Has been treated with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the preceding 8 weeks prior to the first dose of study drug.
5. 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.
6. Female who is pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 150 days after the last dose of subcutaneous study drug and 30 days after the last dose of oral study drug.
7. Male subject who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of oral study drug.
8. Any active, chronic or recurrent invasive infection (e.g., listeriosis and histoplasmosis) and 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). Active 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;
- HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
- HIV: confirmed positive anti-HIV antibody (HIV Ab) test.

9. Subject has active TB or meets TB exclusionary parameters (refer to Section 5.3.1.1 for specific requirements for TB testing).
10. 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).
11. Receipt of any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of oral study drug and including at least 70 days after the last dose of subcutaneous study drug.
12. History of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix.
13. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
14. History of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for GI perforation per investigator judgment.
15. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome.
16. History of demyelinating disease such as Multiple Sclerosis.
17. Subject has been a previous recipient of an organ transplant.

18. History of clinically significant medical conditions or any other reason that in the opinion of the Investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.

19. Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug.

20. 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.

21. 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/1.73m^2;
    - Total white blood cell count (WBC) < 2,500/μL;
    - Absolute neutrophil count (ANC) < 1,500/μL;
    - Platelet count < 100,000/μL;
    - Absolute lymphocyte count < 800/μL;
    - Hemoglobin < 10 g/dL.

22. History of any of the following cardiovascular conditions:

    - moderate to severe congestive heart failure (New York Heart Association class III or IV);
    - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
    - Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
    - Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.

23. Clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 500 msec.

Rationale for Exclusion Criteria

1 – 3	To select the appropriate subject population
6, 7	The impact of upadacitinib on pregnancies is unknown
4, 5, 8 – 23	To ensure safety of the subjects throughout the study

5.2.3 Prior, Concomitant, and Prohibited Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements including folic acid) 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 electronic case report form (eCRF). Also, medications including but not limited to DMARDs taken for RA since date of RA diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF.

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

The AbbVie Therapeutic Area Medical Director identified in Section 6.1.5 *(Serious Adverse event Reporting)* should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Permitted Background RA Therapy

Subjects should continue on their stable (≥ 4 weeks prior to the first dose of study drug) background MTX therapy (restricted to oral or parenteral MTX [15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week]). At any time, the MTX dose may be decreased only for safety reasons. In addition, all subjects 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 MTX or folic acid.

Subjects should also continue on their stable doses of NSAIDs, acetaminophen/paracetamol, oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids.

- 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 starting at Week 26 (after Week 26 assessments have been performed).
- If taking any of the above, including low potency analgesics, i.e., tramadol, codeine, hydrocodone, or propoxyphene 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.

In the event of tolerability (or other safety) issues, the doses of these medications may be decreased or discontinued with substitution of another permitted medication from that class (see Section 5.2.3.2 for prohibited therapies).

PRN use of inhaled corticosteroids is permitted at any time.

Starting at Week 26 (after Week 26 assessments have been performed) and thereafter, two intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids, dosage and frequency per standard of care, are allowed. However, joint injections should be avoided within 21 days prior to the next scheduled study visit to avoid confounding effects of systemic absorption of intra-articular corticosteroids. For the analysis of the TJC and SJC, injected joints will be considered "not assessable" for 3 months from the time of the intra-articular injection.

Starting at Week 26 (after Week 26 assessments have been performed) and thereafter, initiation of or change in corticosteroids, NSAIDs, acetaminophen/paracetamol is allowed as per local label. For RA flare treatment, no more than 3 consecutive days of systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Starting at Week 48 (after Week 48 assessments have been performed) and thereafter initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 9, Section 5.2.1).

5.2.3.2 Prohibited Therapy

JAK Inhibitor

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

Corticosteroids

Oral corticosteroids > 10 mg prednisone/day or equivalent are NOT allowed up to Week 26. Intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids are NOT allowed up to Week 26.

Biologic Therapies

All biologic therapies are prohibited during the study (i.e., Periods 1 and 2).

Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of study population) if they have a) limited exposure (< 3 months), OR b) response to a bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration). Of note: prior exposure to adalimumab (Humira®) is not permitted.

Subjects must have discontinued the bDMARD prior to the first dose of study drug as specified in the washout procedures (Inclusion Criterion 8, Section 5.2.1). For all other bDMARDs, contact the Therapeutic Area Medical Director for the washout period required prior to the first dose of study drug.

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

- Enbrel® (etanercept)
- Remicade® (infliximab)
- Orencia® (abatacept)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Cimzia® (certolizumab pegol)
- Simponi® (golimumab)
- Actemra® (tocilizumab)
- Raptiva® (efalizumab)
- Tysabri® (natalizumab)
- Stelara® (ustekinumab)

- Benlysta® (belimumab)

csDMARD Therapies

Except MTX, subjects must have discontinued all csDMARDs prior to the first dose of study drug as specified in the washout procedures (Inclusion Criterion 9, Section 5.2.1). csDMARD background therapy other than MTX is not allowed during Period 1.

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., Periods 1 and 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 Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Carbamazepine Phenytoin Rifampin Rifapentine St. John's Wort

Opiates

High potency opiates are not permitted during the study (i.e., Periods 1 and 2), and subjects must have discontinued high potency opiates at least 1 week prior to the first dose of study drug, including (but not limited to):

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

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

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap). It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks before first dose of study drug or administered at least 30 days after last dose of oral study drug, or at least 70 days after the last dose of subcutaneous study drug. If the herpes zoster vaccine is to

be administered, and there is no known history of primary varicella (chicken pox), pre-existing immunity to varicella should be confirmed with antibody testing at or prior to screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative the herpes zoster vaccine should not be administered.

If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) 4 weeks before first dose of study drug with appropriate precautions, or administered at least 30 days after last dose of oral study drug, or at least 70 days after last dose of subcutaneous study drug.

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

Traditional oral Chinese medicine is not permitted during the study as these may interfere with upadacitinib metabolism and exposure and may impact efficacy and safety of

upadacitinib treatment. Subjects must have discontinued traditional Chinese medicine at least 4 weeks prior to the first dose of study drug.

5.2.3.3 Rescue Therapy

Rescue therapy will be offered to subjects who meet the following criteria:

Placebo:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects will be switched to blinded upadacitinib treatment regardless of clinical response.

ADA:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded upadacitinib treatment.

Upadacitinib:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ADA treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ADA treatment.

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 ≥ 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 an FSH level > 40 mIU/mL.

If the female subject is < 55 years of age and is not permanently surgically sterile, as defined above, and has had no menses for ≥ 12 months 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 150 days after the last dose of subcutaneous study drug and at least 30 days after the last dose of oral 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.
- 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: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If 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).

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapies. Duration of contraception after discontinuation of csDMARDs should be based on the local label.

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

Additional local requirements may apply. Refer to Appendix C for local requirements (Canada and Korea).

Contraception Recommendation for Males

Based on data from animal studies (including a fertility study) there is no effect of upadacitinib on male reproduction.

For a male subject who is surgically sterile (vasectomy with medical assessment confirming surgical success) OR has a female partner who is postmenopausal or permanently sterile, no contraception is required.

- Condom use and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (for example, using 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 oral 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 recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational

therapies. Duration of contraception after discontinuation of csDMARDs should be based on the local label.

Additional local requirements may apply. Refer to Appendix C for local requirements (Canada and Korea).

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Table 2, Table 3, and Table 4.

Table 2. Study Activities (Period 1)

Activity	Screening D–35 to D–1	BL D1[b]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/ PD[a] D337	30-Day F/U Visit/ Call[c]	70-Day F/U Call[c]
Informed consent[d]	X[d]															
Inclusion/exclusion criteria	X	X														
Medical/surgical history[e]	X	X														
Alcohol and nicotine use	X															
Adverse event assessment[f]	Only SAEs and protocol-related nonserious AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	
Patient questionnaires[h] PtGA Pain (VAS) HAQ-DI Morning Stiffness		X	X	X	X	X	X	X	X	X	X	X	X	X		

Table 2. Study Activities (Period 1) (Continued)

Activity	Screening D–35 to D–1	BL D1[b]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/ PD[a] D337	30-Day F/U Visit/ Call[c]	70-Day F/U Call[c]
Patient questionnaires[h] FACIT-F EQ-5D-5L SF-36 RA-WIS		X				X				X				X		
Latent TB risk assessment form[i]	X													X[i]		
Central lab QuantiFERON-TB Gold test[i] (and/or local PPD skin test)	X													X		
Chest x-ray[j]	X													X		
12-lead ECG[k]	X													X[l]		
X-rays (bilateral hands/feet)	X[m]						X[n]			X[n]				X[n]		
Height (screening only) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam[p]	X	X												X		
Physician Global Assessment (PhGA)		X	X	X	X	X	X	X	X	X	X	X	X	X		

Table 2. Study Activities (Period 1) (Continued)

Activity	Screening D–35 to D–1	BL D1[b]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/ PD[a] D337	30-Day F/U Visit/ Call[c]	70-Day F/U Call[c]
TJC68/SJC66	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum pregnancy test at central lab[q]	X															
Local urine pregnancy test[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central lab tests hsCRP[s] Blood chemistry[t] Hematology (CBC) Urinalysis[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ESR (local lab)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other central lab tests Rheumatoid factor Anti-CCP autoantibodies HBV/HCV screening ANA/dsDNA	X															
HIV central lab[v]	X[v]															
IgG and IgM (central lab)		X			X					X				X		
Blood samples for upadacitinib PK assay			X[w]	X[w]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]	X[x]		

Table 2. Study Activities (Period 1) (Continued)

Activity	Screening D–35 to D–1	BL D1[b]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/ PD[a] D337	30-Day F/U Visit/ Call[c]	70-Day F/U Call[c]
Blood samples for exploratory research and validation studies (optional – see Table 3)[y]		X	X		X					X				X		
Randomization/Drug assignment		X														
Calculation for drug assignment based on TJC/SJC							X[z]	X[z]	X[z]					X[aa]		
CDAI IRT calculation										X[ab,ac]						
Dispense study drug and subject dosing diary		X		X	X	X	X	X	X	X	X	X	X	X[ad]		
Review and copy subject dosing diary and perform drug reconciliation				X	X	X	X	X	X	X	X	X	X	X		

BL = Baseline Visit; CBC = complete blood count; CCP = cyclic citrullinated peptide; D = Day; ECG = electrocardiogram; EQ-5D-5L = EuroQoL-5D; ESR = erythrocyte sedimentation rate; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; F/U = Follow-Up; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; NRS = numerical rating scale; PD = Premature Discontinuation (completely from study [withdrawal of consent]); PhGA = Physician's Global Disease Activity; PK = pharmacokinetics; PPD = purified protein derivative; PtGA = Patient's Global Assessment of Disease Activity; SAE = serious adverse event; SJC = Swollen Joint Count; SF-36 = 36-Item Short Form Health Survey; TB = tuberculosis; TJC = Tender Joint Count; VAS = visual analog scale; Wk = Week

Table 2. Study Activities (Period 1) (Continued)

a. If a subject is prematurely discontinued from study drug, the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation.

b. The Baseline visit procedures will serve as the reference for all subsequent visits with the exception of the ECG and x-rays of hands and feet, which will be obtained at Screening only and used as the baseline reference (see also footnote m regarding x-rays of the hands and feet at Screening).

c. This visit is 30 days after last dose of study drug for those subjects who complete Period 1 and do NOT enter Period 2. A 30-day follow-up phone call may be allowed for subjects who have completed the PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up call to take place 70 days after last dose of subcutaneous study drug for those subjects who complete Period 1 and do NOT enter Period 2 and for those who prematurely discontinue the study (withdrawal of informed consent). The 70 day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

d. Informed consent should be obtained at Screening prior to performing any study related procedures.

e. Note herpes zoster and hepatitis B vaccination status in medical history.

f. Collect serious adverse events and protocol-related nonserious AEs that occur after a subject signs the informed consent, prior to the first dose of study drug.

g. At Week 48 (after Week 48 assessments have been performed), per Investigator judgment, may add or change csDMARDs (concomitant use of up to 2 csDMARDs, except the combination of MTX and leflunomide, or increasing csDMARD dose).

h. Prior to other procedures.

i. Complete the latent TB risk assessment form annually. Refer to Section 5.3.1.1. Study Procedures TB Testing for specific requirements for TB testing and TB Prophylaxis.

j. The screening chest x-ray will not be required if a subject had a previous normal chest-x-ray within 90 days of Screening, provided that all source documentation is available at the site (refer to Section 5.3.1.1 Chest X-Ray for specific requirements). At Week 48, obtain chest x-ray for subjects with newly identified TB risk factors based on the TB risk assessment form, or 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.

k. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all source documentation is available. Refer to Section 5.3.1.1 12-Lead ECG for additional details.

l. All subjects will have an ECG at Week 48 and PD visit as applicable.

m. Subjects are eligible for the study if the locally read screening x-rays confirm at least one of the following: ≥ 3 bone erosions on x-ray OR ≥ 1 bone erosion combined with a positive RF OR ≥ 1 bone erosion combined with positive anti-CCP autoantibodies. Screening x-rays will serve as baseline x-rays for scoring purposes. Refer to Section 5.3.1.1 Study Procedures X-Rays of Hands and Feet for additional details.

n. Week 14 x-rays of hands and feet will be performed for all subjects who do not meet $\geq 20\%$ improvement in TJC and SJC compared to baseline. X-rays of hands and feet will be performed for all subjects at Week 26 and Week 48. Refer to Section 5.3.1.1 Study Procedures X-Rays of Hands and Feet for additional details.

o. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

p. A full physical exam is required at the visits indicated. A symptom-directed physical exam may be performed when necessary.

Table 2. Study Activities (Period 1) (Continued)

q. For all females of childbearing potential, collect serum for pregnancy test at screening. If serum pregnancy test comes back borderline, a repeat test ≥ 3 days later is necessary to document continued lack of positive result (pregnancy is an exclusion criterion). Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.

r. For all females of childbearing potential, collect urine for pregnancy test at Baseline and all subsequent visits. 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 the study. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.

s. Central lab hsCRP results will remain blinded to the Sponsor, Investigator, study site personnel, and the subject for all visits except Screening. 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. Any local hsCRP or local CRP tests should not be reported to the investigator until treatment allocation is unblinded.

t. 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.

u. 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.

v. Anti-HIV Ab will be performed at Screening, unless prohibited by local regulations. 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.

w. At Week 2 and Week 4 visits, PK samples (plasma) should be collected prior to oral drug dosing and the subjects should take the oral study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study oral 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.

x. PK samples should be collected at any time during the visit. Subject should follow the regular dosing schedule.

y. Samples only collected if subject provides written consent.

z. Subjects in the placebo group who do not achieve ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 will be switched to blinded upadacitinib treatment. At Week 26, all placebo subjects will be switched to blinded upadacitinib treatment regardless of response. Subjects in the ADA group who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment. At Week 26, all remaining subjects in the ADA group who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded upadacitinib treatment. Subjects in the upadacitinib group who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ADA treatment. At Week 26, all remaining subjects in the upadacitinib group who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ADA treatment.

Table 2. Study Activities (Period 1) (Continued)

aa. Starting at Week 48, subjects who failed to show at least 20% improvement in both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

ab. Refer to Section 5.2.3.3.

ac. CDAI calculation requires input of SJC + TJC (based on a 28 joint count) + PtGA + PhGA into IRT system.

ad. For subjects entering Period 2.

Note: Visit window is ± 3 days for the first 30 weeks and ± 7 days for the remainder of Period 1. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator. Subjects who choose to discontinue study drug treatment, but continue to participate in the study, should complete a Premature Discontinuation Visit (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, PK sample collection, and blood sample collection for optional exploratory research and validation studies. In addition, after discontinuing study drug, all rescue and efficacy-driven discontinuation criteria no longer apply; this includes 20% TJC/SJC calculations at Weeks 14 – 22, and Week 48 and thereafter, as well as CDAI calculation at Week 26, if applicable.

Table 3. Study Activities – Optional Samples for Exploratory Research and Validation Studies (Period 1 Only)

Activity	Screening D –35 to D –1	BL D1[a]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/PD D337
Pharmacogenetic samples[a,b]	--	X	--	--	--	--	--	--	--	--	--	--	--	--
Epigenetic samples[b]	--	X	X	--	X	--	--	--	--	X	--	--	--	X
Transcriptomic and epigenetic samples[b]	--	X	X	--	X	--	--	--	--	X	--	--	--	X
Plasma samples for proteomic and targeted protein investigations[b]	--	X	X	--	X	--	--	--	--	X	--	--	--	X
Serum samples for proteomic and targeted protein investigations[b]	--	X	X	--	X	--	--	--	--	X	--	--	--	X

BL = Baseline Visit; D = Day; F/U = Follow-up; PD = Premature Discontinuation; Wk = Week

a. The sample is preferred to be collected at BL, but can be drawn at any time during the subject's participation.

b. Based on the value of the different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches. Samples may be used for assay of study drugs if needed.

Note: Collections to be performed only if subject provides separate written consent to collect the exploratory research/validation studies samples; if the separate consent is not signed, no samples can be collected. The separate written consent may be part of the main consent form.

Table 4. Study Activities (Period 2)

Activity	Wk 60	Wk 72	Wk 84	Wk 96	Monthly	Every 12 Weeks Until Study Completion[a]	Every 24 Weeks Until Study Completion[a]	Every 48 Weeks Until Study Completion[a]	Every 96 Weeks Until Study Completion[a]	Final/ PD Visit	30-Day F/U Visit / Call[b]	70-Day F/U Call[b]
Adverse event assessment	X	X	X	X		X				X	X	X
Concomitant therapy	X	X	X	X		X				X	X	
Patient questionnaires[c] PtGA Pain (VAS) HAQ-DI Morning stiffness	X	X	X	X		X				X		
Latent TB risk assessment form				X				X				
Central lab QuantiFERON-TB Gold test[d] (and/or local PPD skin test)				X[d]				X[d]				
Chest x-ray[e]				X[e]				X[e]				
12-lead ECG[f]				X[f]				X[f]		X[f]		
X-rays (bilateral hands/feet)[g]				X[g]					X[g]			
Vital signs and body weight[h]	X	X	X	X		X				X	X	
Physical exam[i]		X		X			X[i]			X		
Physician Global Assessment (PhGA)	X	X	X	X		X				X		
TJC68/SJC66	X	X	X	X		X				X		

Table 4. Study Activities (Period 2) (Continued)

Activity	Wk 60	Wk 72	Wk 84	Wk 96	Monthly	Every 12 Weeks Until Study Completion[a]	Every 24 Weeks Until Study Completion[a]	Every 48 Weeks Until Study Completion[a]	Every 96 Weeks Until Study Completion[a]	Final/ PD Visit	30-Day F/U Visit / Call[b]	70-Day F/U Call[b]
Local urine pregnancy test[j]	X	X	X	X		X				X	X	
In-home urine pregnancy test[k]					X							
Central lab tests hsCRP[l] Blood chemistry[m] Hematology (CBC) Urinalysis[n]	X	X	X	X		X				X	X	
ESR (local lab)	X	X	X	X		X				X		
Calculation for drug assignment based on TJC/SJC	X[o]	X[o]	X[o]	X[o]		X[o]						
Dispense study drug and subject dosing diary	X	X	X	X		X						
Review and copy subject dosing diary and perform drug reconciliation	X	X	X	X		X				X		

CBC = complete blood count; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; ECG = electrocardiogram; F/U = Follow-Up; HAQ-DI = Health Assessment Questionnaire – Disability Index; hsCRP = high-sensitivity C-reactive protein; NRS = numerical rating scale; PD = Premature Discontinuation; PhGA = Physician's Global Disease Activity; PPD = purified protein derivative; PtGA = Patient's Global Assessment of Disease Activity; RCT = randomized controlled trial; SAE = serious adverse event; SJC = Swollen Joint Count; TB = tuberculosis; TJC = Tender Joint Count; VAS = visual analog scale; Wk = Week

a. Every 12, 24, 48, or 96 weeks from the Week 96 visit.

b. This visit is 30 days after last dose of study drug for those subjects who complete Period 2. A 30-day follow-up phone call and a 70-day follow-up phone call may be allowed for subjects who have completed PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Table 4. Study Activities (Period 2) (Continued)

c. Prior to other procedures.

d. TB testing should be performed every 48 weeks after Week 96 in subjects with previous negative QuantiFERON-TB Gold and/or PPD tests. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines. Refer to Section 5.3.1.1, Study Procedures, TB Testing for specific requirements for TB testing and TB Prophylaxis. Study drug(s) should not be withheld at the time of the first positive TB test.

e. Obtain chest x-ray every 48 weeks after Week 96 for subjects with newly identified TB risk factors based on the TB risk assessment form, or 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.

f. ECGs will be performed every 48 weeks after Week 48. An ECG may be performed at any visit if deemed necessary by the Investigator.

g. X-rays of hands and feet must be performed at Week 96 and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous [redacted] weeks.

h. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

i. A full physical exam is required every 24 weeks after Week 96. A symptom-directed physical exam may be performed when necessary.

j. 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. Pregnant subjects must discontinue from study drug treatment. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.

k. Starting at Week 48, for women of childbearing potential, in-home urine pregnancy tests will be performed monthly.

l. hsCRP results will remain blinded to Sponsor, Investigator and study site personnel, and the subject for all visits until the last subject reaches the end of Period 1.

m. 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.

n. Dipstick urinalysis will be completed by the central lab at all required visits. 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.

o. Starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

Note: Visit window is ± 7 days for Period 2. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator. Subjects who choose to discontinue study drug treatment, but continue to participate in the study, should complete a Premature Discontinuation Visit (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, PK sample collection, and blood sample collection for optional exploratory research and validation studies. In addition, after discontinuing study drug, all rescue and efficacy-driven discontinuation criteria no longer apply; this includes 20% TJC/SJC calculations at Week 48 and thereafter.

5.3.1.1 Study Procedures

The study procedures outlined in Table 2 and Table 4 are discussed in detail in this section, with the exception of exploratory research and validation studies (discussed in Section 5.3.1.2), 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 for the study (i.e., includes both Periods 1 and 2) 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. Subjects can withdraw informed consent at any time.

Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

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-RA-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 RA-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.

Patient Questionnaires

Subjects will complete the following questionnaires as specified in Table 2 and Table 4; a validated translation will be provided in their local language, as applicable:

Period 1

- Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS) (Appendix G)
- Patient's Assessment of Pain Visual Analog Scale VAS (Appendix H)
- Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess the physical function and health-related quality of life of each subject (Appendix I)
- Patient's Assessment of Severity and Duration of Morning Stiffness Numerical Rating Scale (NRS) (Appendix J)*
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (Appendix K)
- EuroQoL-5D-5L (EQ-5D-5L) (Appendix L)
- Short Form-36 (SF-36) (Appendix M)
- Work Instability Scale for RA (RA-WIS) (Appendix N)

Period 2

- Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS) (Appendix G)
- Patient's Assessment of Pain Visual Analog Scale VAS (Appendix H)

- Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess the physical function and health-related quality of life of each subject (Appendix I)
- Patient's Assessment of Severity and Duration of Morning Stiffness Numerical Rating Scale (NRS) (Appendix J)*

* Paper; all other patient-reported outcomes (PROs) 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.

TB Testing/TB Prophylaxis

The TB screening tests provide 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 F) and tested for TB infection by QuantiFERON-TB Gold test. 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 site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF. The TB risk assessment form will be completed annually for all subjects, regardless of TB test results.

If a subject had a negative PPD 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. These cases may be discussed with the AbbVie TA MD. The results of the TB test(s) will be retained at the site as the original source documentation.

Subjects with a negative TB test and chest x-ray (CXR) not suggestive of active TB or prior TB exposure may be enrolled.

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 chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Any positive TB screen after the patient 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 test:

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD 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 are positive, the TB test is considered positive.
- The PPD Skin Test (also known as a TB Skin Test or Mantoux 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).

- 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 NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD are required per local guidelines) the PPD will be performed. 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 have an ulcerating reaction to the PPD in the past should not be re-exposed and the PPD should be considered positive.
- 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 patient 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 who reside 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 chest x-ray 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 chest x-ray not suggestive of active TB need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie Therapeutic Area Medical Director 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 a latent TB, 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 needs to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Of Note: Rifampicin or Rifapentine is 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 within 1 year prior to first study drug administration will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

Subjects with a documented completion of a full course of anti-TB therapy greater than 1 year prior to first study drug administration may be allowed to enter the study only after consultation with the AbbVie Therapeutic Area Medical Director.

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. TB prophylaxis should be initiated and study drug(s) should not be withheld. Two to

four 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.

Chest X-Ray (CXR)

A CXR (posterior-anterior 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 (every 48 weeks) for subjects with newly identified TB risk factors based on the TB risk assessment form (Appendix F), or 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 pulmonologist 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 Therapeutic Area Medical Director before enrolling the subject.

12-Lead ECG

A resting 12-lead ECG will be performed at the designated study visits as specified in Table 2 and Table 4. 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 Therapeutic Area Medical Director 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.

X-Rays of Hands and Feet

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

Handling of X-Rays of Hands and Feet at Screening

The x-ray inclusion criterion is defined as follows: $\geq$ 3 bone erosions on x-ray OR $\geq$ 1 bone erosion and a positive rheumatoid factor OR $\geq$ 1 bone erosion and a positive anti-CCP autoantibody.

Screening x-rays of bilateral hands (posterior-anterior view) and bilateral feet (anteroposterior view) must be performed within the 35-day screening period.

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. Subjects can receive first dose of study drug after the x-rays have been determined to be of sufficient quality by the central imaging laboratory.

Screening x-rays of hands and feet will serve as baseline x-rays for scoring purposes.

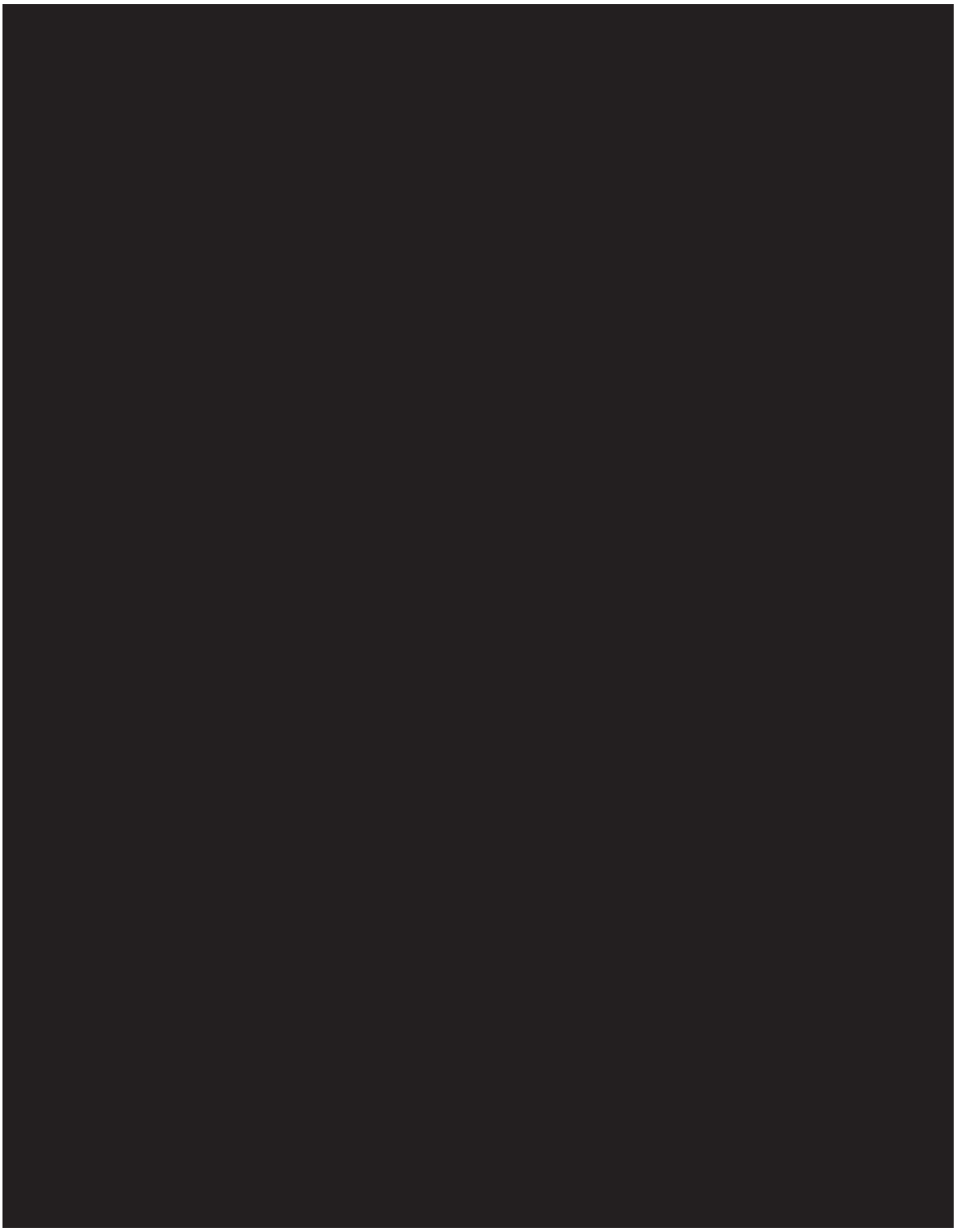
Handling of X-Rays of Hands and Feet after Baseline

Handling of x-rays of hands and feet after baseline in Period 1 is illustrated in Figure 3.

Week 14 x-rays of hands and feet will be performed for all non-responders (regardless of treatment group) (Figure 3, box A). Non-responders at Week 18 and non-responders at Week 22 will not have x-rays.

All subjects (regardless of response) will have Week 26 x-rays (Figure 3, box B) and Week 48 x-rays (Figure 3, box C).

If a subject prematurely discontinues the study and/or study drug, depending on the time of discontinuation, new x-rays of hands and feet may be needed.



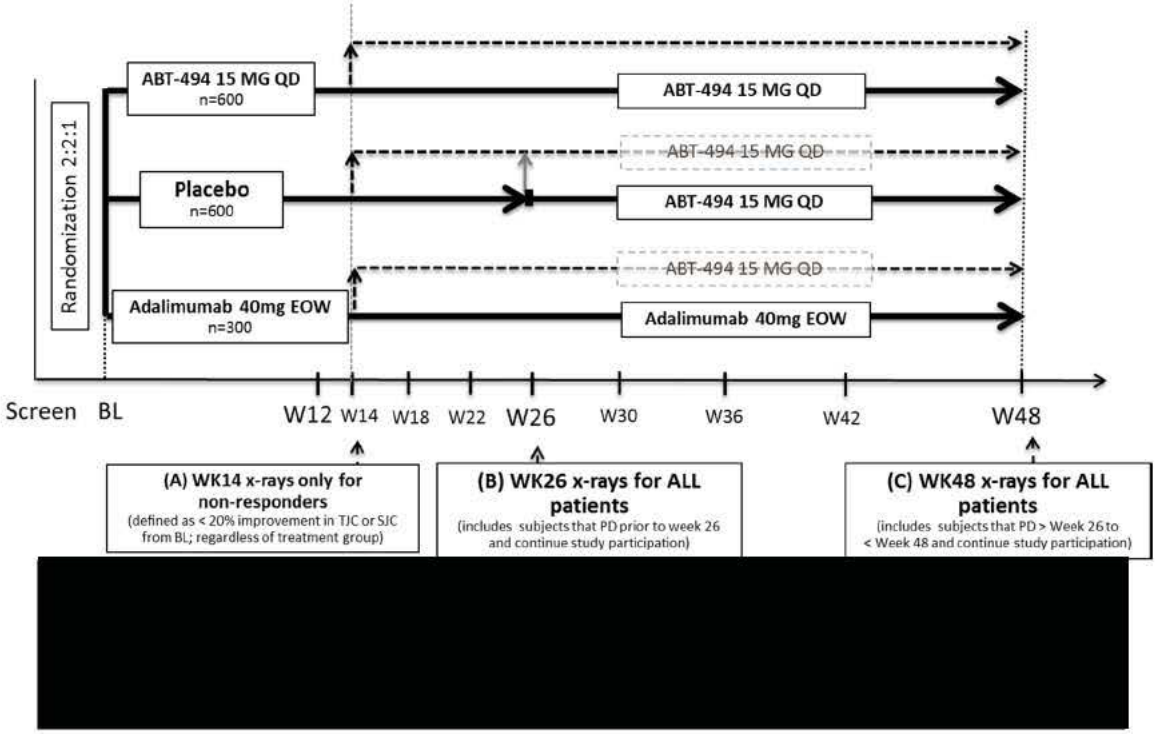
[redacted]

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 the IAG/Site Operations Manual. X-rays not meeting the quality requirements must be repeated.

Overall in Period 1, each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 14 (only for non-responders at Week 14), Week 26, and Week 48/PD; in addition, subjects who prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint.

In Period 2, a follow-up x-ray of hands and feet is planned at Week 96 and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous [redacted] weeks. Images will be sent to the central imaging laboratory designated by the Sponsor.

Figure 3. Handling of X-Rays of Hands and Feet after Baseline (Period 1)



BL = baseline; eow = every other week; PD = premature discontinuation; QD = once daily; SJC = swollen joint count; TJC = tender joint count; WK = week

Height and Weight

Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits as specified in Table 2 and Table 4. All measurements will be recorded in metric units where applicable.

Vital Signs

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 Table 2 and Table 4. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Table 2 and Table 4. 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 (see Section 6.1.1.1 for AE definition). 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.

Physician Global Assessment of Disease Activity Visual Analog Scale (VAS)

At visits specified in Table 2 and Table 4, the Physician will rate global assessment of subject's current disease activity ranging from 0 to 100 independent of the subject's self-assessment using the VAS, which consists of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed (Appendix D).

TJC and SJC Assessment

TJC Assessment

An assessment of 68 joints (Appendix E) will be done for tenderness by pressure manipulation on physical examination at visits specified in Table 2 and Table 4. Joint pain/tenderness will be classified as: present ("1"), absent ("0"), replaced ("9") or no assessment ("NA").

SJC Assessment

An assessment of 66 joints (Appendix E) will be done by directed physical examination at visits specified in Table 2 and Table 4. 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 joints will be considered as "not assessed" ("NA") for 3 months 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 a qualified medical professional (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.

CDAI

The CDAI calculation is required to determine if a subject fails to achieve low disease activity at the Week 26 visit. An Interactive Response Technology (IRT) will calculate CDAI with input from site personnel on joint counts and the subject's and physician's Global Assessment of RA Disease Activity score. A worksheet will be provided to capture the components required for IRT entry to obtain the CDAI calculation.

The calculation used to determine CDAI score at Week 26 is as follows:

$$CDAI = TJC28 + SJC28 + PtGA + PhGA$$

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 urine pregnancy test at post-baseline 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

the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later) to document continued lack of a positive result.

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 5. 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 Table 2 and Table 4. Blood draws should be performed only after all clinical assessments and questionnaires (HAQ DI, Patient's Assessment of Pain, etc.) 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 Table 2 and Table 4. 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. Other laboratory abnormalities, including those which meet the toxicity management criteria outlined in Section 6.1.7 *(Toxicity Management)*, may be recorded as AEs at the discretion of the investigator.

Table 5. 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 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	Central Lab Tests: 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] Rheumatoid Factor[e] Anti-CCP autoantibodies[e] ANA and dsDNA (reflex) autoantibodies[e] hs-CRP[h] IgG and IgM FSH[i] MRB Panel[j] Local Lab Tests Urine pregnancy test[k] ESR

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bHCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CCP = cyclic citrullinated peptide; CK-MB = creatine kinase-MB isozymes; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; 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; hsCRP = high sensitivity C-reactive protein; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; MRB = minimal residual B-cells; PCR = polymerase chain reaction; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell

a. 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.

b. 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.

Table 5. Clinical Laboratory Tests (Continued)

c. INR will only be measured if ALT and/or AST > 3 × ULN.
d. A serum pregnancy test will be performed for all female subjects at the Screening Visit and if postbaseline urine pregnancy test turns positive.
e. At Screening only.
f. Anti-HIV Ab will be performed at Screening, unless prohibited by local regulations. 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 starting from Baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, and the subject.
i. At screening for female subjects < 55 years old with no menses for ≥ 12 months AND no history of permanent surgical sterilization.
j. If needed to assess B cell counts in subjects who have recently discontinued rituximab, see Inclusion Criterion 8, Section 5.2.1.
k. 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 minimum at monthly intervals (either at study visits or at home between scheduled study visits). (for details see Section 5.3.1.1 (Study Procedures).

Hepatitis Screen

All subjects will be tested for the presence of HBV and HCV at Screening.

Hepatitis B:

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

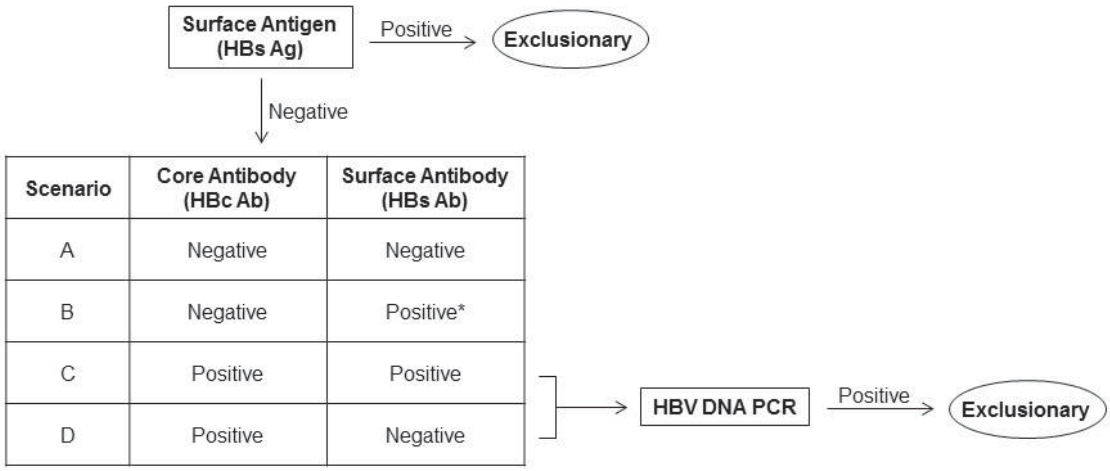
- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

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 4, 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 4, Scenario B).*
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 4, Scenarios C and D).
  - A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.

Figure 4. Criteria for HBV DNA PCR Qualitative Testing



* For subjects who have had a HBV vaccination (should be documented in the medical history), a positive test result for HBs Ab is expected and these subjects may be enrolled.

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. If required by country regulatory authorities to confirm eligibility, subjects should be tested for antibodies to HIV at Screening. This testing is to be done at the central lab. 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.

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.

Subjects will be randomized in a 2:2:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: Upadacitinib (ABT-494) 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg eow) (N = 300)

Randomization will be stratified by prior bDMARD exposure (yes or no) and geographic region.

See Section 5.5.3 for details.

Study Drug Dispensing, Dosing, and Compliance

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Table 2 and Table 4. 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 Table 2 and Table 4, 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.

ADA/placebo for ADA study drug can be administered to subjects by study site medical staff or designee (subject, friend, family member, or health care professional) during the visit at Baseline. Subjects or a designated family member or friend will be trained to administer study drug at this 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

In Period 1, 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 our understanding of how individuals respond to drugs and our ability to predict which subjects would benefit from receiving specific therapies. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor RA by assessing associations between disease characteristics, outcomes data, and biomarkers of interest.

Validation studies, including those related to the development of potential in vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

AbbVie (or people or companies working with AbbVie) will store the biomarker 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 RA and related conditions continues, but for no longer than 20 years after study completion.

DNA Samples for Pharmacogenetic or Epigenetic Analyses

Whole blood samples for DNA isolation will be collected at the visits indicated in Table 3 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 DNA extraction and/or long-term storage or analyses. Instructions for the preparation and shipment of the pharmacogenetic and/or epigenetic research samples will be provided in a laboratory manual.

RNA Samples for Transcriptomic and/or Epigenetic Analyses

Whole blood samples for RNA isolation will be collected at the visits indicated in Table 3 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 RNA extraction and/or long-term storage or analyses. Instructions for the preparation and shipment of the samples will be provided in a laboratory manual.

Serum and Plasma Samples for Systemic Analyses, Including but Not Limited to Proteomic and Metabolomic

Serum and plasma samples will be collected at the visits indicated in Table 3 from each subject who consents to provide samples for exploratory/validation research. These samples may be used for assay of study drugs 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 and Anti-Drug Antibody Measurements

5.3.2.1 Collection of Samples for Analysis

Blood Samples for Upadacitinib PK Assay

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

- At Weeks 2 and 4 prior to dosing;
- At Weeks 8, 12, 14, 18, 22, 26, 30, 36, 42 and 48/PD at any time during the visit.

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

For all PK samples, 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 Period 1 Variables

5.3.3.1.1 Primary Variables

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response at Week 12 (US/FDA regulatory purposes) or the proportion of subjects achieving CR based on DAS28 (CRP) at Week 12 (EU/EMA regulatory purposes). Analyses will be conducted separately for US/FDA regulatory purposes and EU/EMA regulatory purposes; for each set of analysis, only one primary endpoint is specified.

ACR20 response rate will be determined based on 20% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQ-DI, or hsCRP.

CR is defined as DAS28 (CRP) < 2.6.

5.3.3.1.2 Key Secondary Variables

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

1. Change from baseline in DAS28 (CRP) at Week 12;
2. Change from baseline in mTSS at Week 26;

3. Change from baseline in HAQ-DI at Week 12;
4. ACR50 response rate at Week 12 (non-inferiority of upadacitinib vs ADA);
5. Change from baseline in SF-36 Physical Component Score (PCS) at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12;
7. Proportion of subjects achieving CR based on DAS28 (CRP) at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12;
9. Change from baseline in morning stiffness at Week 12;
10. Change from baseline in FACIT-F at Week 12;
11. ACR50 response rate at Week 12 (superiority of upadacitinib vs. ADA);
12. Change from baseline in Patient's Assessment of Pain at Week 12 (superiority of upadacitinib vs. ADA);
13. Change from baseline in HAQ-DI at Week 12 (superiority of upadacitinib vs. ADA).

Other key secondary endpoints (upadacitinib versus placebo) for US/FDA regulatory purposes are:

- ACR50 response rate at Week 12
- ACR70 response rate at Week 12
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

1. Change from baseline in modified Total Sharp Score (mTSS) at Week 26;
2. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12;

3. Change from baseline in DAS28 (CRP) at Week 12;
4. Change from baseline in HAQ-DI at Week 12;
5. ACR20 response rate at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of upadacitinib versus ADA);
7. Change from baseline in SF-36 PCS at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12
9. Change from baseline in morning stiffness at Week 12;
10. Change from baseline in FACIT-F at Week 12.
11. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26;

Other key secondary endpoints (upadacitinib versus placebo) for EU/EMA regulatory purposes are:

- ACR50 response rate at Week 12
- ACR70 response rate at Week 12

ACR20/50/70 response rates will be determined based on 20%/50%/70% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQ-DI, or hsCRP.

5.3.3.1.3 Additional Variables

Additional endpoints (upadacitinib versus placebo and adalimumab) at all visits are:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;

- Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in CDAI and SDAI;
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and CDAI criteria (see below);
- Change from baseline in morning stiffness;
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.22;
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3;
- ACR/EULAR Boolean remission.

	DAS28 (CRP) and DAS28 (ESR)	SDAI	CDAI
LDA	≤ 3.2	≤ 11.0	≤ 10
CR	< 2.6	≤ 3.3	≤ 2.8

Additional endpoints at Weeks 12, 26, and 48 are:

- Change from baseline in SF-36;
- Change from baseline in FACIT-F.
- Change from baseline in RA-WIS.
- Change from baseline in EQ-5D-5L.

Additional endpoints at Weeks 26 and 48 are:

- Change from baseline in modified Total Sharp Score (mTSS);
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS ≤ 0);
- Change from baseline in joint space narrowing score and joint erosion score.

5.3.3.2 Period 2 Variables

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 60, 72, 84, 96, and every 12 weeks thereafter until completion of the study:

- ACR20/50/70 response rates;
- Change from baseline in individual ACR components;
- Change from baseline in DAS28 (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in CDAI and SDAI;
- Change from baseline in morning stiffness;
- Proportion of subjects achieving LDA and the proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria (as defined for Period 1);
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3;
- Concomitant corticosteroid use (systemic use and intra-articular injections);
- ACR/EULAR Boolean remission.

Additionally, assessment for the evaluation of radiographic changes in Period 2 will occur at Week 96 and every 96 weeks thereafter (or Premature Discontinuation visit):

- Change from baseline in modified Total Sharp Score (mTSS);
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS of ≤ 0);
- Change from baseline in Radiographic joint space narrowing and erosion scores.

5.3.4 Safety Variables

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, ECG, 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 Table 2. 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 known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to nucleic acids, proteins, lipids, or metabolites.

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. Theses assessments may be explored in the context of RA or related conditions and/or upadacitinib or drugs of similar classes. 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 develop new therapies, research methods or technologies. In addition, samples from this study may be stored for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

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 disease progression or 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, which rule out continuation of the study drug, as determined by the Investigator or the AbbVie Therapeutic Area Medical Director.
- Serious infections (e.g., sepsis) which 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 study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Therapeutic Area Medical Director.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie Therapeutic Area Medical Director.
- 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 diagnosed with lupus-like syndrome, multiple sclerosis, or demyelinating disease.

- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation as determined by the Investigator.
- Subject develops a gastrointestinal perforation.
- Subjects with disease progression or not responding to treatment are to be withdrawn from the trial based on investigator's discretion.
- Starting at Week 48, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) must be discontinued from study drug.

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment or study participation should complete a Premature Discontinuation visit (PD visit) as described in Section 5.1 (Overall Study Design and Plan: Description)

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

There are two active study drugs in this study. The first is daily upadacitinib (ABT-494) and the second is ADA eow.

Upadacitinib (ABT-494) (or matching placebo) study drug will be taken orally once daily, 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. Subjects will continue their weekly stable background therapy of MTX. AbbVie will not supply MTX nor folic acid (or equivalent, such as folinic acid).

ADA (or matching placebo) will be provided as a subcutaneous injection solution in 1 mL pre-filled syringes containing ADA 40 mg/0.8 mL (or matching placebo). ADA (or matching placebo) will be subcutaneously administered eow at approximately the same time of day.

Subjects should take a dietary supplement of oral folic acid beginning on Day 1 (Baseline) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions.

Subjects will receive both oral study drug QD (either upadacitinib (ABT-494) 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo). When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 6.

Table 6. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib (ABT-494)	oral	tablet	15 mg	AbbVie
Upadacitinib (ABT-494) matching placebo	oral	tablet	NA	AbbVie
Adalimumab	subcutaneous injection	Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	40 mg/ 0.8 mL	AbbVie or Vetter
Adalimumab matching placebo	subcutaneous injection	Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	NA	AbbVie or Vetter

5.5.2.1 Packaging and Labeling

Upadacitinib (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.

ADA will contain 2 pre-filled syringes of ADA 40 mg/0.8 mL or matching placebo per carton. 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 Drugs

Upadacitinib (ABT-494) must be stored at controlled room temperature (15° to 25°C/59° to 77°F). ADA must be stored protected from light at 2° – 8°C (36° – 46°F). Study drug must not be frozen at any time. The investigational products are for investigational use only and are 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 2:2:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: Upadacitinib (ABT-494) 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg eow) (N = 300)

Subjects will receive both oral study drug QD (either upadacitinib 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo) until the study is unblinded.

Randomization will be stratified by prior bDMARD exposure (yes or no) and geographic region.

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).

Upadacitinib/Placebo (daily dosing):

- If a subject should forget to take their upadacitinib (ABT-494) (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 > 14 consecutive days during the first 26 weeks, > 21 days between Week 26 and Week 48 or > 30 consecutive days during Period 2 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from study drugs. If study treatment drug is interrupted or withdrawn in Periods 1 or 2, both oral and subcutaneous study drug administration must be stopped.

ADA/Placebo (biweekly dosing):

- Biweekly ADA (or matching placebo) should be injected the same day and approximately the same time every other week. If the subject should forget to inject their subcutaneous study drug on their regularly scheduled dosing date, they should inject the forgotten dose as soon as they remember the dose was missed up to the day before their scheduled dose. The subject must not administer two injections on the same day.
- If the subject experiences a study drug interruption of > 2 consecutive missed doses during the first 26 weeks or > 3 consecutive missed doses after Week 26 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from the study. If study treatment drug is interrupted or withdrawn in Periods 1 or 2, both oral and subcutaneous injections must be stopped.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personnel with direct oversight, conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), will remain blinded to each subject's treatment through Week 26. The Investigator, study site personnel, and the subject will remain blinded to each subject's treatment in Period 1 until the last subject completes the last visit of Period 1 (Week 48).

In order to maintain the blind, the upadacitinib (ABT-494) tablets and placebo tablets, and ADA syringes and placebo syringes 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 Therapeutic Area Medical Director prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie Therapeutic Area Medical Director, 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 Therapeutic Area Medical Director, AbbVie requests that the AbbVie Therapeutic Area Medical Director 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.

When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

5.5.5.2 Blinding of Data for Data Monitoring Committee

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.

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 includes two periods.

Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active-comparator controlled study to compare safety and efficacy of upadacitinib 15 mg QD versus placebo and versus ADA 40 mg eow in subjects with moderately to severely active RA who are on a on a stable background of MTX and who have an inadequate response to MTX. Period 1 is designed to test superiority of upadacitinib versus placebo for achieving the primary endpoint (ACR20 at Week 12 for US/FDA regulatory purposes or the proportion of subjects achieving CR based on DAS28 [CRP] at Week 12 for EU/EMA regulatory purposes), and other secondary efficacy parameters.

The purpose of Period 2 is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib (15 mg QD) in RA subjects who have completed Period 1. All subjects will continue treatment to which they were assigned at the end of Period 1. This will allow assessments of long-term safety of upadacitinib without compromising the study conduct or results of ongoing Period 1. In addition, the study design will allow the assessment of the maintenance of treatment response of both study drugs during this extension study.

When the last subject completes the last visit of Period 1 (Week 48), study drug assignment will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Adalimumab was first approved in the United States and European Union for the treatment of RA in 2002 and 2003, respectively, and is considered standard of care. Additional updates regarding approved indications and safety can be found in the current edition of the Package Insert and Summary of Product Characteristics.

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 RA. 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 moderately to severely active RA patients who have had an inadequate response to prior MTX treatment. Key entry criteria are to enroll adult female and male subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA. Eligible study subjects must have ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at Screening. Subjects must have been on oral or parenteral MTX therapy for ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week).

5.6.4 Selection of Doses in the Study

One dose of the once-daily formulation of upadacitinib will be evaluated: upadacitinib 15 mg QD. The dose selection in this study is based on extrapolation of pre-clinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the

Phase 1 studies in healthy volunteers (single and multiple ascending dose Studies M13-401 and M13-845, respectively) and Phase 2 studies in RA subjects (Studies M13-537 and M13-550). The dose selected for Study M14-465, upadacitinib 15 mg QD, dosed up to 5 years, is expected to be efficacious with an acceptable safety profile.

The 15 mg QD dose using the once-daily formulation provides equivalent daily AUC and comparable C_{max} and C_{min} to 6 mg BID of the immediate-release formulation tested in Phase 2 studies in subjects with RA. In Phase 2 studies, the 6 mg BID dose was shown to achieve the near maximum efficacy.

6.0 Complaints

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

The investigational product in this trial contains both a biologic compound and a device component (pre-filled syringe, pen).

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 other cause(s) 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, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during the 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 case report form.

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
- Herpes Zoster
- Tuberculosis
- Malignancy (all types)
- Gastrointestinal Perforations
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
- Lipid Profile Changes
- Anemia
- Neutropenia
- Lymphopenia
- Increased serum creatinine and renal dysfunction
- Hepatic events and increased hepatic transaminases
- Elevated creatine phosphokinase (CPK)
- Embolic and thrombotic events (non-cardiac, non-CNS)

6.1.2 Adverse Event Severity

The Investigator will classify adverse events according to the Rheumatology Common Toxicity Criteria v.2.0 (Appendix O).[22]

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.

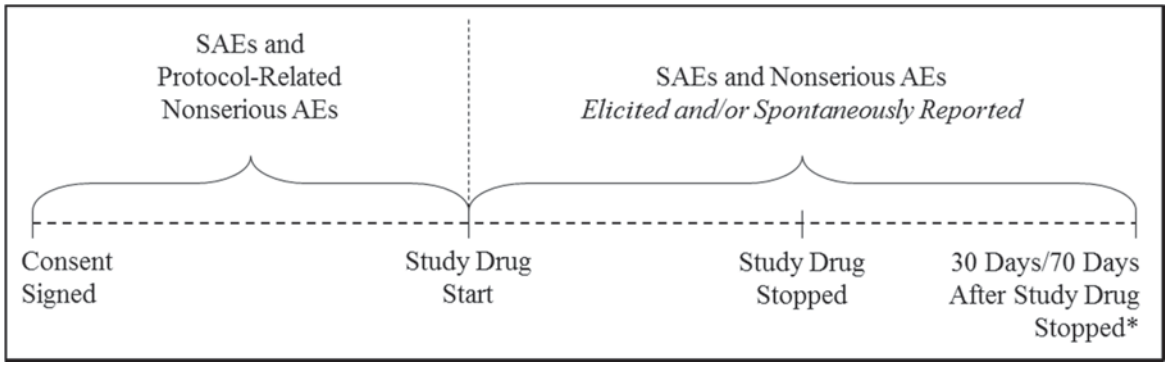
If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until 70 days following discontinuation of subcutaneous study drug administration and until 30 days following the discontinuation of oral 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 non-serious AEs collected for the remainder of the study participation. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 5.

Figure 5. Adverse Event Collection



* 30 days after the last dose of oral study drug; 70 days after the last dose of subcutaneous study drug.

Additionally, in order to assist the adjudication process, additional information on any potential MACE will be collected, if applicable.

In the case of any of the following reported events, an appropriate supplemental MACE eCRF should be completed:

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

In the case of any of the following AEs, the corresponding Supplemental AE eCRF should be completed:

- Hepatic;
- Renal;
- Herpes Zoster Infection;
- CPK increases considered by the investigator to be an AE;
- Embolic and thrombotic events (non-cardiac, non-CNS)..

6.1.5 Serious Adverse Event Reporting

AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events, and those events with a long latency. AbbVie is participating in an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects/patients who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event.

In the event of an SAE, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to subcutaneous study drug or not, the physician will notify Clinical Pharmacovigilance within 24 hours of the physician becoming aware of the event by entering the SAE or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. SAEs and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® EDC system or if RAVE® is not operable, should be documented on the SAE non-case report form (CRF) forms and emailed (preferred route) or faxed to the Clinical Pharmacovigilance within 24 hours of being made aware of the SAE.

Email:	[redacted]	
FAX to		

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email:

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

Primary Therapeutic Area Medical Director:

[redacted]

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

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 countries will be the most current version of the Investigator's Brochure for upadacitinib and/or the Summary of Product Characteristics (SmPC) for ADA, as applicable.

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 from study drug (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject or the partner of an enrolled subject and the outcome of the pregnancy will be collected. Pregnancies in study subjects will be collected from the date of the first dose through 150 days following the last dose of subcutaneous study drug. Pregnancies will be collected from the first dose of oral study drug through 30 days following the last dose of oral study drug for female subjects and female partners of male subjects.

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 an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 150 days after the last subcutaneous study drug administration. Male and female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last oral study drug administration. Male subjects should refrain from donating sperm for up to 30 days post last dose of oral study drug. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit. 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.

For subjects who discontinued study drug but continued study participation and are instead 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 the first 26 weeks, more than 21 days between Weeks 26 and 48 or more than 30 consecutive days thereafter, the subject must be discontinued from study drug. Subjects who develop active TB must be permanently discontinued from study drug.

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of

gastrointestinal perforation. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued from study drug.

Cardiovascular Events: Subjects presenting with potential cardiovascular events should be carefully monitored. These events will be reviewed and adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner.

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.

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, 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 7 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. If a repeat test is required per Table 7, the repeat testing must occur as soon as possible.

Table 7. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• 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)	• 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)	• 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	• 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	• 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 7. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5. o A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug immediately if confirmed ALT or AST > 3 × 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%). • Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • Interrupt study drug immediately if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF. • Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within 1 week: o ALT > 5 × ULN OR o ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR o ALT or AST > 3 × ULN along with clinical signs of possible hepatitis A positive result for HBV DNA PCR testing in these subjects will require immediate interruption of study drug and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and > 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 ≤ 1.5 × baseline value and ≤ ULN. • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
Creatine Phosphokinase	• If confirmed CPK ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD For the above CPK elevation scenarios, complete supplemental CPK eCRF.

For allowed study drug interruption, the following rules apply:

Period 1

- Upadacitinib/Placebo (daily dosing):
  - Allow study drug interruption ≤ 14 consecutive days for AEs and surgery during the first 26 weeks;
  - After Week 26, study drug interruption due to AEs/surgery is allowed ≤ 21 days.
- Adalimumab/Placebo (biweekly dosing):
  - Allow study drug interruption ≤ 2 consecutive missed doses for AEs and surgery during the first 26 weeks;
  - After Week 26, study drug interruption due to AEs/surgery is allowed ≤ 3 consecutive doses.
- If the subject must undergo emergency surgery, study drug should be interrupted at the time of the surgery.
- Elective surgery during the first 26 weeks is discouraged and needs to be discussed with the AbbVie Therapeutic Area Medical Director.
- If the subject undergoes elective surgery, the subcutaneous study drug should be interrupted two weeks prior to the planned surgery and the oral study drug should be interrupted 1 week prior to the planned surgery.
- After 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

- Upadacitinib/Placebo (daily dosing):
  - Up to 30 consecutive days of oral study drug interruption is allowed.
- Adalimumab/Placebo (biweekly dosing):
  - Study drug interruption due to AEs/surgery is allowed ≤ 3 consecutive doses.

- If the subject undergoes elective surgery, the subcutaneous study drug should be interrupted 2 weeks prior to the planned surgery and the oral study drug should be interrupted 1 week prior to the planned surgery.
- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of surgery.
- After 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 (example: 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 adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. 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 Contacts:

Primary Contact: Alternate Contact:

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.

Examples of protocol deviations include the following:

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Unless otherwise specified, statistical tests will be at two-sided significance level of 0.05 for efficacy analyses and all other analyses. A test will be deemed significant if the *P* value is less than or equal to 0.05 unless otherwise specified.

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of

Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

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 Week 26 analysis. 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 (FAS)

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 meet any major protocol violations during the study. Definitions of major protocol violations will be detailed in the SAP. Additional analysis may be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol violations.

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, separately for Period 1 and Period 2: 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

Separately for Period 1 and Period 2, 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 for Period 1 alone as well as for Period 1 and Period 2 combined. The exposure to study drug (days) will be summarized with the mean, standard deviation, median, and range for each treatment group.

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 in Period 1 divided by the number of tablets a subject is supposed to take each day times the length of time that the subject was in the Treatment Phase.

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 in Period 1.

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 by 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 with a start date 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 during study drug exposure 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 Efficacy Analysis for Period 1

8.1.4.1.1 Primary Efficacy Variables

The primary endpoint in Period 1 (at Week 12) for US/FDA regulatory purposes is listed in Section 5.3.3.1.1. The primary endpoint in Period 1 (at Week 12) for EU/EMA regulatory purposes is also listed in Section 5.3.3.1.1. Analyses will be conducted separately for US/FDA regulatory purposes and EU/EMA regulatory purposes; for each set of analysis, only one primary endpoint is specified.

Analysis of the primary endpoint will be conducted on the FAS based on treatment as randomized. For the ACR20 and CR comparison between the upadacitinib group and the placebo group, Cochran-Mantel-Haenszel test adjusting for main stratification factors will be used. For the primary analysis of ACR20 and CR response at Week 12,

Non-Responder Imputation (NRI) will be used. In addition, sensitivity analysis will be done using Observed Cases (OC). Supportive analysis will also be conducted on the Per Protocol Analysis Set.

The primary efficacy analyses will be performed in demographic subgroups including age, gender, weight, body mass index, race, 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.

8.1.4.1.2 Key Secondary Efficacy Variables

Key secondary endpoints in for US/FDA regulatory purposes are listed in Section 5.3.3.1.2. Key secondary endpoints in for EU/EMA regulatory purposes are also listed in Section 5.3.3.1.2.

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 EU/EMA purposes, analysis will be conducted to test the non-inferiority of upadacitinib versus ADA for LDA response rate at Week 12 using the 95% confidence interval of treatment difference against a non-inferiority margin of 10%. For ACR50 response rate at Week 12, similar analysis of non-inferiority will be conducted for US/FDA purposes. Superiority of upadacitinib vs ADA will also be tested for LDA and ACR50.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Between-group comparisons for the upadacitinib treatment group and the placebo treatment group will be performed using the ANCOVA model with treatment groups as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates. For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of upadacitinib vs adalimumab will also be tested.

See Section 8.1.4.1.5 for imputation methods.

8.1.4.1.3 Other Efficacy Variables

Additional efficacy variables are listed in Section 5.3.3.1.3 and will be summarized for all visits, including visits beyond Week 12. For binary endpoints, frequencies and percentages will be reported for each treatment group. For continuous endpoints, the change from baseline mean, standard deviation, median, and range will be reported for each treatment group.

8.1.4.1.4 Multiplicity Control for the Primary and Ranked Key Secondary Endpoints

In order to preserve Type I error, a step-down approach will be used to test the primary and ranked 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.

8.1.4.1.5 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, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

Multiple Imputation (MI): The MI analysis impute missing data multiple times under appropriate random variation and thus generate multiple imputed "pseudo-complete" datasets. Results will be aggregated across the multiple imputed datasets, overcoming drawbacks of the single imputation methods.

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

Linear Extrapolation for Radiographic Data: For radiographic data (i.e., mTSS-based endpoints), if a subject is rescued at Week 14 to a different study drug or prematurely discontinued study drug, their Week 26/48 data will be imputed assuming a linear relationship between baseline and previous x-ray collected at the time of rescue/PD.

For non-radiographic data, the NRI approach will serve as the primary analysis approach for key binary endpoints. The MI approach will serve as the primary analysis approach for key continuous endpoints. For radiographic data, analysis based on both linear extrapolation and an as-observed analysis (where the as-observed Week 26/48 assessments for all subjects are used) will be conducted.

8.1.4.2 Long-Term Efficacy for Period 1 and Period 2 Combined

The efficacy endpoints of long-term efficacy analysis are listed in Section 5.3.3.2 and will be summarized for all visits.

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 Analyses

8.1.5.1 General Considerations

Safety analyses will be carried out using the Safety Analysis Set. Analyses will be conducted for both short term and long term.

Safety analyses are based on treatments actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from baseline in vital signs, physical examination results,

and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from baseline to defined time points will be tabulated.

Missing safety data will not be imputed.

8.1.5.2 Analysis of Adverse Events

Unless otherwise specified, the following conventions apply for both short term and long term safety analysis.

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 70 days following the last dose of study drug for subjects on ADA and AEs starting more than 30 days following the last dose of study drug for subjects on upadacitinib or placebo will not be included in summaries of TEAEs. For subjects who continued into Period 2, the AEs that are reported in Period 2 will be summarized in the long term safety analysis.

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 2% of subjects or more in any treatment group);
- Frequent reasonably possibly related AEs (reported in 2% 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 Clinical and Safety as deemed appropriate.

TEAEs will be summarized and presented by system organ classes (SOCs) and preferred terms (PTs) using MedDRA. The SOCs 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 serious infection, opportunistic infection, herpes zoster, TB, gastrointestinal perforations, malignancies, MACE, renal dysfunction, anemia, increased CPK, non-cardiac, non-CNS embolic and thrombotic events, and drug-related hepatic disorders) will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the combined safety analysis of Period 1 and Period 2.

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

8.1.5.2.2 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, Vital Sign, and ECG Data

Changes from baseline by visit 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 in Period 1.

The laboratory data will be categorized as Grade 1, Grade 2, Grade 3, and Grade 4 according to OMERACT criteria (Rheumatology Common Toxicity Criteria v.2.0). For creatine phosphokinase, and serum creatine, NCI CTC criteria will be used. The shift

tables will tabulate the number and percentage of subjects with baseline and post-baseline values by grade levels.

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 for upadacitinib using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The structure of the starting PK model will be based on the PK analysis of data from previous studies. 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 evaluation criteria described below will be used to examine the performance of different models.

1. The objective function of the best model is significantly smaller than the alternative model(s).
2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).

3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base PK model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using non-linear mixed-effects modeling. The relationship between these conditional estimates 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 of renal function, etc.) will be explored using stepwise forward selection method, or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary PK parameters with various covariates will be explored.

Relationships between upadacitinib exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored. The relationship between exposure (e.g., population PK model predicted average concentrations, area under the curve, trough concentrations, the individual model-predicted PK profiles, or some other appropriate measure of exposure) and drug effect will be explored. Several classes of models (e.g., linear, log-linear, exponential, E_{max}, sigmoid E_{max}, etc.) will be evaluated to characterize the exposure-response relationship based on observed data. 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 RA, rather than in the CSR.

Additional analyses may be conducted if useful and appropriate.

8.2 Determination of Sample Size

The planned total sample size of 1500 for this study (with a 2:2:1 randomization ratio) provides at least 90% power for a 22% difference in ACR20 response rate (assuming a placebo ACR20 response rate of 37%) at two-sided significance level of 0.05 and accounting for a 10% dropout rate. It will also provide at least 90% power for a 19.3% difference in CR response rate (assuming a placebo CR response rate of 6.2%). With the given sample size, there is also approximately 90% power to detect a treatment difference of 0.39 in change from baseline in mTSS at Week 26 with a standard deviation of 2, at two-sided significance level of 0.05 and accounting for a 10% dropout rate. This sample size will also provide at least 90% power for testing non-inferiority of upadacitinib versus ADA in LDA or ACR 50 response rate at Week 12 with a non-inferiority margin being 10%, assuming 35% and 40% LDA or ACR 50 response rates for ADA and upadacitinib, respectively. It will also provide at least 90% power in testing superiority of upadacitinib versus placebo for most of the key secondary endpoints, including change from baseline in DAS28 (CRP), change from baseline in HAQ-DI, ACR50 and ACR70 response rate, and SF-36 (PCS), 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 2:2:1 ratio to one of the three treatment groups (Upadacitinib 15 mg QD, placebo and ADA 40 mg eow) stratified by prior bDMARD exposure (yes or no) and geographic region.

See Section 5.5.3 for details.

9.0 Ethics

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

Good Clinical Practice requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent, and all other forms of subject information

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

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

Any 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 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.

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.

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

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

10.2 Case Report Forms

Case report forms (CRFs) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an EDC system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

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

The Investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

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.

Patient 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 Patient:
    - Patient Global Assessment of Disease Activity VAS
    - Patient's Assessment of Pain VAS
    - HAQ-DI
    - SF-36
    - FACIT-F
    - RA-WIS
    - EQ-5D-5L
  - Completed by Site:
    - Physician Global Assessment of Disease Activity VAS
- The following data will be completed by the patient on paper and entered into the EDC system:
  - Patient's Assessment of Morning Stiffness

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 will be maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the trial. This access will be available for the duration of the trial 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 method:

Tablet Based

- The instrument/scale will be collected electronically via a tablet 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 CRF Health. 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, CRF, 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 CRF 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 CRF and corrected on-line. 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 rheumatoid factor, anti-CCP, and HBV/HCV testing, will be conducted using a central laboratory (refer to Table 2 and Table 4). 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 Table 2 and Table 4). 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 exploratory research/validation studies 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 exploratory research/validation studies may be provided to investigators and used in scientific publications or presented at medical conventions. Exploratory research/validation studies 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 and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator must retain any records related to the study according to local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug, and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products 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 Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)
Protocol Date:	01 December 2017

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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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
[redacted]	[redacted]	Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacokinetics and Pharmacodynamics
		Bioanalysis
		Clinical Program Development
		Clinical Program Development

Appendix C. Local Requirements

Canada

Section 5.2.1, Inclusion Criteria

12. If female of childbearing potential, must be practicing at least two reliable methods of contraception (one highly effective method combined with one effective method, refer to Section 5.2.4), that are effective from Study Day 1 through at least 150 days after the last dose of subcutaneous study drug, through at least 30 days after the last dose of oral study drug, and through 180 days after the last dose of methotrexate. If more than one of the above intervals apply, the longest interval must be adhered to.
13. If male, and subject is sexually active with the female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of oral study drug and through 90 days after the last dose of methotrexate, to practice the protocol-specified contraception (refer to Section 5.2.4). The same intervals apply to abstention from sperm donation. If more than one of the above intervals apply, the longest interval must be adhered to.

Section 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 ≥ 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 an FSH level > 40 mIU/mL.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to use two forms of contraception. This includes one form of highly effective contraception and one effective method of contraception. That is effective from Study Day 1 (or earlier) through at least 150 days after the last dose of subcutaneous study drug, through at least 30 days after the last dose of oral study drug, and through 180 days after the last dose of methotrexate. If more than one of the above intervals apply, the longest interval must be adhered to:

- Highly effective methods:
  - Hormonal contraceptives started at least 2 months prior to randomization (e.g., combined [estrogen and progestogen containing] [oral contraceptives, patch, vaginal ring, injectables, and implants);
    - Intrauterine device (IUD) or intrauterine system (IUS);
    - Vasectomy and tubal ligation.
- Effective methods:
  - Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)
  - Note: The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception. When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Male and female condoms should not be used together as they can tear or become damaged.

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 oral study drug and through 90 days after the last dose of methotrexate to practice contraception with:

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

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 30 days after the last dose of oral study drug and through 90 days after the last dose of methotrexate.

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.

Korea

Section 5.2.1, Inclusion Criteria

9. Except for MTX, subject must have discontinued all csDMARDs. The washout period for csDMARDs prior to the first dose of study is specified below or should be at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
   - ≥ 8 weeks prior to first dose of study drug for leflunomide, if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days

with colestyramine, or 30 days washout with activated charcoal or as per local label).

Section 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 ≥ 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 an FSH level > 40 mIU/mL.

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 150 days after the last dose of subcutaneous study drug and through at least 30 days after the last dose of oral 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.
- 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).

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.

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapies. Duration of contraception after discontinuation of csDMARDs should be based on the local label.

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 oral 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).

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 30 days after the last dose of oral 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 recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapies. Duration of contraception after discontinuation of csDMARDs should be based on the local label.

Hong Kong, Korea, Malaysia, Singapore and Taiwan

Section 5.2.1, Inclusion Criteria

3. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 10 to 25 mg/week (or ≥ 7.5 mg/week in subjects intolerant of MTX at doses ≥ 10 mg/week) for ≥ 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation.

Appendix D. Physician's Global Assessment of Disease Activity Example

Visual Analog Scale (VAS)

VAS will be used to assess the physician's global assessment of disease activity and the subject's assessment of pain. The VAS consists of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed:

- *Physician's global assessment of disease activity (current status)*
  The Physician will rate global assessment of subject's current disease activity ranging from 0 to 100 (see example below)

Mark the line below to indicate the subject's rheumatoid arthritis disease activity (independent of the subject's self-assessment).

0	100
Very Low	Very High

Appendix E. Joint Evaluation Worksheet Example

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

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

Appendix F. 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:
   - Sub-Saharan Africa
   - India
   - China
   - Mexico
   - Southeast Asia or Micronesia
   - The former Soviet Union
3. Have you lived or worked in a prison, homeless shelter, immigration center, 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
   - Production of Sputum
   - Blood-Streaked Sputum
   - 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 G. Patient's Global Assessment of Disease Activity Example

Visual Analog Scale (VAS)

VAS will be used to assess the subject's global assessment of disease activity. Each VAS consists of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed:

- *Subject's global assessment of disease activity (within last 24 hours)*
  The subject will rate the severity of the RA symptoms and how he/she is doing from 0 to 100. This assessment will be used for the DAS28 (CRP) calculation in this study (see example below):

Please place a vertical mark on the line below to indicate how well your rheumatoid arthritis has been doing during THE LAST 24 HOURS:

0 — 100
Very Well — Very Poorly

Appendix H. Patient's Assessment of Pain Example

Visual Analog Scale (VAS)

VAS will be used to assess the subject's assessment of pain. Each VAS consists of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed:

How much pain have you had because of your condition within the previous week?

Place a mark on the line below to indicate how severe your pain has been.

NO PAIN ——————————————————— **WORST POSSIBLE PAIN**

Appendix I. Health Assessment Questionnaire (HAQ-DI) Example

HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your illness affects your ability to function in daily life.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

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

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

☐ Cane
☐ Walker
☐ Crutches
☐ Wheelchair
☐ Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)
☐ Built up or special utensils
☐ Special or built up chair
☐ Other (Specify: _____)

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

☐ Dressing and Grooming ☐ Eating

☐ Arising ☐ Walking

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open jars which have been previously opened?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

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

☐ Raised toilet seat ☐ Bathtub bar

☐ Bathtub seat ☐ Long-handled appliances for reach

☐ Jar opener (for jars previously opened) ☐ Long-handled appliances in bathroom

☐ Other (Specify: _____)

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

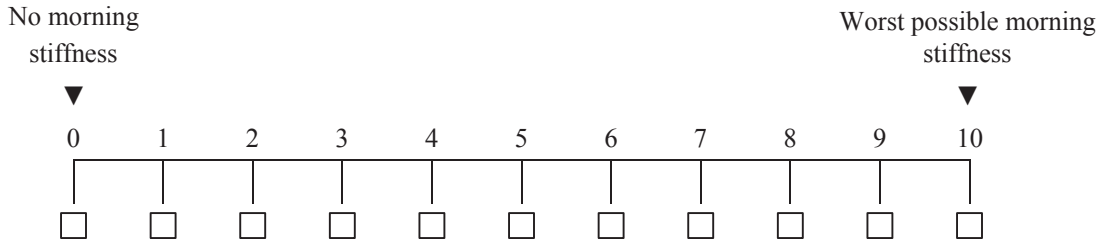
☐ Hygiene	☐ Gripping and opening things
☐ Reach	☐ Errands and chores

HAQ – United States/English
HAQ-DI_AU1.0-eng-USori.doc ® Stanford University

Appendix J. Patient's Assessment of Morning Stiffness Example

Instructions:

Please clearly mark an 'x' in the box (☒) that best describes your experience with **morning stiffness** on awakening in the **past 7 days**.



When you experience morning stiffness, how long does it take to get as limber as possible: ___hours ____ minutes

Appendix K. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scale Example

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)
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16 November 2007
Page 1 of 1

Appendix L. EuroQoL-5D-5L Example

Under each heading, please check the ONE box that best describes your health TODAY:

Mobility

I have no problems walking	☐
I have slight problems walking	☐
I have moderate problems walking	☐
I have severe problems walking	☐
I am unable to walk	☐

Self-Care

I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

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

I have no problems with doing my usual activities	☐
I have slight problems with doing my usual activities	☐
I have moderate problems with doing my usual activities	☐
I have severe problems with doing my usual activities	☐
I am unable to do my usual activities	☐

Pain/Discomfort

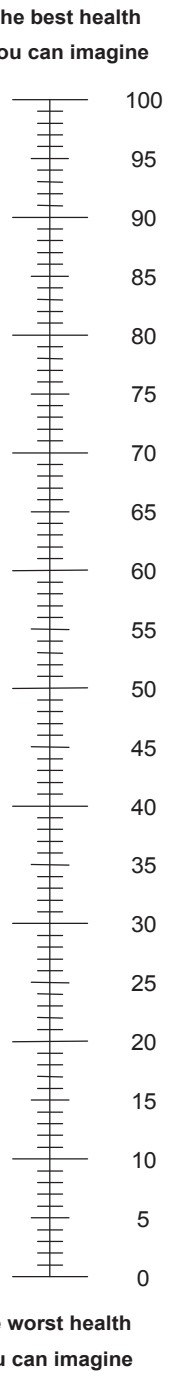
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/Depression

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

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix M. Short Form-36 (SF-36™) Health Status Survey Questionnaire Example

Your Health and Well-Being

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

THANK YOU FOR COMPLETING THESE QUESTIONS

Appendix N. RA-WIS Example

Work Instability Score For Rheumatoid Arthritis

On the following page you will find some statements, which have been made by people who have rheumatoid arthritis. We would like you to tick "yes" if the statement applies to you, and tick "no" if it does not. Please choose the response that applies best to you at the moment.

	Yes	No
1. I'm getting up earlier because of the arthritis	☐Y Yes	☐N No
2. I get very stiff at work	☐Y Yes	☐N No
3. I'm finding my job is about all I can manage	☐Y Yes	☐N No
4. The stress of my job makes my arthritis flare	☐Y Yes	☐N No
5. I'm finding any pressure on my hands is a problem	☐Y Yes	☐N No
6. I get good days and bad days at work	☐Y Yes	☐N No
7. I can get my job done, I'm just a lot slower	☐Y Yes	☐N No
8. If I don't reduce my hours I may have to give up work	☐Y Yes	☐N No
9. I am very worried about my ability to keep working	☐Y Yes	☐N No
10.I have pain or stiffness all the time at work	☐Y Yes	☐N No
11.I don't have the stamina to work, like I used to	☐Y Yes	☐N No
12.I have used my holiday so that I don't have to go sick	☐Y Yes	☐N No
13.I push myself to go to work because I don't want to give in to the arthritis	☐Y Yes	☐N No
14.Sometimes I can't face being at work all day	☐Y Yes	☐N No
15.I have to say no to certain things at work	☐Y Yes	☐N No
16.I've got to watch how much I do certain things at work	☐Y Yes	☐N No
17.I have great difficulty opening some of the doors at work	☐Y Yes	☐N No
18.I have to allow myself extra time to do some jobs	☐Y Yes	☐N No
19.It's very frustrating because I can't always do things at work	☐Y Yes	☐N No
20.I feel I may have to give up work	☐Y Yes	☐N No
21.I get on with the work but afterwards I have a lot of pain	☐Y Yes	☐N No
22.When I'm feeling tired all the time work's a grind	☐Y Yes	☐N No
23.I'd like another job but I am restricted to what I can do.	☐Y Yes	☐N No

Appendix O. Rheumatology Common Toxicity Criteria v.2.0 Example

For designation of adverse event terms not shown in the Rheumatology Common Toxicity Criteria v.2.0 table, the approach described in Row 1 should be used.

Rheumatology Common Toxicity Criteria v.2.0 **Based on Woodworth TG, et al. Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for Anti-Rheumatic Therapies**				
	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation, or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalised > 24 hr Study drug discontinued
A. Allergic/Immunologic				
A1. Allergic reaction/ hypersensitivity (includes drug fever)	Transient rash: drug fever < 38°C: transient, asymptomatic bronchospasm	Generalised urticaria responsive to meds; or drug fever > 38°C, or reversible bronchospasm	Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/pharyngeal oedema, requiring resuscitation
A2. Autoimmune reaction	Seriologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anaemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med. required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g., oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy

A. Allergic/Immunologic (continued)				
A5. Vasculitis	Localised, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g., oral corticosteroids)	Generalised, parenteral corticosteroids required or/and short duration hospitalisation	Prolonged, hospitalisation, ischemic changes, amputation
B. Cardiac				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalisation required, parenteral meds
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g., 1 + feet/calves), self-limited, no therapy required	Symptomatic (e.g., 2 + feet/calves), requires therapy	Symptoms limiting function (e.g., 3 + feet/calves, 2 + thighs), partial relief with treatment prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, transient increase by > 20 mmHg (diastolic) or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100 or by > 10 mmHg (diastolic), requiring and responding readily to treatment	Symptomatic increase > 150/100, > 20 mmHg, persistent, requiring multi agency therapy, difficult to control	Hypertensive crisis
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure > 20 mmHg	Symptomatic, without interference with function, recurrent or persistent > 20 mmHg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischaemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrthymia or/and CHF

B. Cardiac (continued)				
B7. Pericarditis/ pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic NSAID required	Detectable on chest x-ray, dyspnoea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery
B8. Phlebitis/thrombosis/ Embolism (excludes injection sites)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism
C. General (Constitutional)				
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7° – 38.5°C	Symptomatic, recurrent 38.6° – 39.9°C. Relieved by meds.	≥ 40°C; ≤ 24 h, persistent symptoms; partial response to meds.	≥ 40°C, debilitating, > 24 h, hospitalisation; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.
C4. Insomnia	Difficulty sleeping, short term, no interfering with function	Difficulty sleeping interfering with function, use of prescription med.	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalisation; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalisation; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring IV fluids/hospitalization > 24 hrs
C7. Weight gain	5% – 9.9%	10% – 19.9%	20% – 30%	NA
C8. Weight loss	5% – 9.9%	10% – 19.9%	20% – 30%	NA

D. Dermatologic				
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete, or irreversible even if patchy
D2. Bullous eruption	Localised, asymptomatic	Localised, symptomatic, requiring treatment	Generalised, responsive to treatment; reversible	Prolonged, generalised, or requiring hospitalisation for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1 – 2 wks) controlled with emollients	Generalised, interfering with ADL > 2 wks, persistent pruritis, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain, pruritis, < few days	Erythema, pain, oedema, may include superficial phlebitis, 1 – 2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery
D5. Petechiae (without vasculitis)	Few, transient asymptomatic	Dependent areas, persistent up to 2 wks	Generalised, responsive to treatment; reversible	Prolonged, irreversible, disabling
D6. Photosensitivity	Transient erythema	Painful erythema and oedema requiring topical treatment	Blistering or desquamation, requires systematic corticosteroids	Generalised exfoliation or hospitalisation
D7. Pruritis	Localised, asymptomatic, transient, local treatment	Intense, or generalised, relieved by systematic medication	Intense or generalised; poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/popular eruption; pruritis transient; TOC or no meds	Diffuse macular/popular eruption or erythema with pruritus; dry desquamation; treatment required	Generalised, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalisation; or parenteral corticosteroids
D9. Indurartion/ fibrosis/Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and not disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms
E. Ear/Nose/Throat				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery

E. Ear/Nose/Throat (continued)				
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, slowly reversible	Requires enteral support; residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	NA
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis)	Intermittent hoarseness, able to vocalise	Persistent hoarseness, able to vocalise	Whispered speech, slow return of ability to vocalise	Unable to vocalize for extended
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition
F. Eye/Ophthalmologic				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA
F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight

F. Eye/Ophthalmologic (continued)				
F5. Vision changes (e.g., blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophtalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight
G. Gastrointestinal				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2 – 3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4 – 6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g., incontinence, severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤ 2 units needed; responds to treatment	Haematemesis, transfusion 3 – 4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation
G6. Haematochezia (rectal bleeding)	Haemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion > 3 – 4 units	> 4 units, hypotension, requiring hospitalization

G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent > 2 wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma
G8. Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management
G9. Pancreatitis	Anylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatitic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required.
H. Musculoskeletal				
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalisation required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, responds to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non-narcotic); minor effects on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds

I. Neuropsychiatric				
I1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation or danger to self
I2. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events	Cerebrovascular vascular accident with permanent disability
I3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily routine	Debilitating/disabling and permanent; toxic psychosis
I4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obundation, stupor	Coma
I5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	NA
I6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA
I7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	NA
I8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis
I9. Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paraethesias interfering with function	NA
I10. Seizure	NA	Recurrence of old seizures, controlled with adjustment of medication	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures

I. Neuropsychiatric				
I11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalization
J. Pulmonary				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O2 relieves	Symptomatic at rest, debilitating, requires constant nasal O2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitation, requiring hospitalisation
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity – DLCO)	76% – 90% of pre-treatment value	51% – 75% of pre-treatment value	26% – 50% of pre-treatment value	≤ 25% of pre-treatment value

Laboratory Data				
K. Haematology				
K1. Hgb (g/dl) decrease from pre-treatment	1.0 – 1.4	1.5 – 2.0	2.1 – 2.9, or Hgb < 8.0, > 7.0	≥ 3.0; or Hgb < 7.0
K2. Leukopenia (total WBC) × 1000	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	< 1.0
K3. Neutropenia (× 1000)	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	< 0.5
K4. Lymphopenia (× 1000)	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	< 0.5
K5. Platelets (× 1000)	75 – LLN	50 – 74.9	20 – 49.9; platelet transfusion required	< 20; recurrent platelet transfusions
L. Chemistry				
L1. Hypercalcaemia (mg/dl)	1.1 × ULN – 11.5	11.6 – 12.5	12.6 – 13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycemia (mg/dl) Fasting	140 – 160	161 – 250	251 – 500	> 500, or associated with ketoacidosis
L3. Hyperkalaemia (mg/dl)	5.5 – 5.9	6.0 – 6.4	6.5 – 7.0 or any ECG change	> 7.0 or any arrhythmia
L5. Hypocalcaemia (mg/dl)	0.9 × LLN – 7.8	7.7 – 7.0	6.9 – 6.5; or associated with symptoms	< 6.5 or occurrence of tetany
L6. Hypoglycemia (mg/dl)	55 – 64 (no symptoms)	40 – 54 (or symptoms present)	30 – 39 (symptoms impair function)	< 30 or coma
L7. Hyponatraemia (mg/dl)	--	125 – 129	120 – 124	< 120
L8. Hypokalaemia (mg/dl)	--	3.0 – 3.4	2.5 – 2.9	< 2.5

L. Chemistry				
L9. CPK (also if polymyositis-disease)*	1.2 – 1.9 × ULN	2.0 – 4.0 × ULN	4.0 × ULN with weakness but without life-threatening signs or symptoms	> 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening
L10. Serum uric acid	1.2 – 1.6 × ULN	1.7 – 2.9 × ULN	3.0 – 5.0 × ULN or gout	NA
L11. Creatinine (mg/dl)*	1.1 – 1.3 × ULN	1.3 – 1.8 × ULN	1.9 – 3.0 × ULN	> 3.0 × ULN
L12. SGOT (AST)	1.2 – 1.5 × ULN	1.6 – 3.0 × ULN	3.1 – 8.0 × ULN	> 8.0 × ULN
L13. SGPT (ALT)	1.2 – 1.5 × ULN	1.6 – 3.0 × ULN	3.0 – 8.0 × ULN	> 8.0 × ULN
L14. Alkaline phosphatase	1.1 – 2.0 × ULN	1.6 – 3.0 × ULN	3.0 – 5.0 × ULN	> 5.0 × ULN
L15. T. bilirubin	1.1 – 1.4 × ULN	1.5 – 1.9 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN
L16. LDH	1.3 – 2.4 × ULN	2.5 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
M. Urinalysis				
M1. Haematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusion required
M2. Proteinuria (per 24 h)	300 – 500 mg (tr/1+)	501 – 1999 mg (2+)	2 – 5.0 g (3+) nephrotic syndrome	5.0 g (4+) anasarca
M3. WBC in urine	NA	NA	Indicating acute interstitial nephritis	Associated with acute renal failure
M4. Uric acid crystals	Present without symptoms	NA	With stones or symptoms of stones (e.g., renal colic)	Causing renal outflow obstruction and hospitalization

OTC = over-the-counter medication; ADL = activities of daily living; IV = intravenous; ECG = electrocardiogram; CHF = congestive heart failure; MRI = magnetic resonance imaging; Hb = haemglobin; LLN = lower limit of normal; ULN = upper limit of normal; WBC = white blood cells; SLE = systemic lupus erythematosus; ANA = antinuclear antibodies; H-2 blockers = histamine-2 blockers; FVC = forced vital capacity

* For CPK and Creatinine NCI CTC grading will be used. For CPK the following gradings apply: Grade 1: > ULN – 2.5 × ULN; Grade 2: > 2.5 – 5.0 × ULN; Grade 3: > 5.0 – 10.0 × ULN; Grade 4: > 10.0 × ULN; For Creatinine the following gradings apply: Grade 1: > 1 – 1.5 × Baseline; > ULN – 1.5 × ULN; Grade 2: > 1.5 – 3.0 × Baseline; > 1.5 – 3.0 × ULN; Grade 3: > 3.0 baseline; > 3.0 – 6.0 × ULN; Grade 4: > 6.0 × ULN

Appendix P. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Global Protocol Change

"ABT-494" has been changed to read "Upadacitinib" or "Upadacitinib (ABT-494)" throughout the protocol.

Specific Protocol Changes:

Section 1.0 Title Page
"Sponsor:" previously read:

Sponsor:	AbbVie* [redacted] 1 North Waukegan Road North Chicago, IL 60064

Has been changed to read:

Sponsor:	AbbVie* 1 North Waukegan Road North Chicago, IL 60064

Section 1.0 Title Page
"Sponsor/Emergency Contact:"
Add: Emergency 24 hour Number: [redacted]

Sponsor/Emergency Contact:	[redacted]

Has been changed to read:

Sponsor/Emergency Contact:	[redacted]

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-465
Name of Study Drug: ABT-494	**Phase of Development:** 3
Name of Active Ingredient: ABT-494	**Date of Protocol Synopsis:** 11 January 2017
Protocol Title: A Phase 3, Randomized, Double-Blind Study Comparing ABT-494 to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)	
Objectives: **Period 1** 1. To compare the efficacy of ABT-494 15 mg once daily (QD) versus placebo, and versus adalimumab (ADA) for the treatment of signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA who are on a stable background of methotrexate (MTX) and who have an inadequate response to MTX (MTX-IR). 2. To compare the efficacy of ABT-494 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR). 3. To compare the safety and tolerability of ABT-494 15 mg QD versus placebo, and versus ADA in subjects with moderately to severely active RA subjects who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR). **Period 2** To evaluate the long-term safety, tolerability, and efficacy of ABT-494 15 mg QD in subjects with RA who have completed Period 1.	
Investigators: Multicenter	
Study Sites: Approximately 510	

Study Population: Adult female and male subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP) ≥ 5 mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week).
Number of Subjects to be Enrolled: Approximately 1500

Methodology:

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of ABT-494 15 mg QD versus placebo and versus ADA for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of MTX and have an inadequate response to MTX (MTX-IR). Period 1 is also designed to compare the efficacy of ABT-494 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability and efficacy of ABT-494 15 mg QD in subjects with RA who have completed Period 1.

The study duration will include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes the last visit of the double-blind treatment period) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: ABT-494 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg every other week [eow]) (N = 300)

Subjects will receive both oral study drug QD (either ABT-494 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo) until the study is unblinded.

Subjects must have been on oral or parenteral MTX therapy for ≥ 3 months, on a stable MTX dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week), and must remain on a stable dose throughout the study; the MTX dose may be decreased only for safety reasons. In addition, all subjects should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Starting at the Week 26 visit (after Week 26 assessments have been performed), initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, and csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label.

Subjects with prior exposure to at most one biologic disease-modifying anti-rheumatic drug (bDMARD) (except ADA) for RA may be enrolled in the study (up to 20% of total number of subjects) after the required washout period is satisfied and if they have a) limited bDMARD exposure (< 3 months), OR b) response to a bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration). These subjects will be equally stratified across all treatment groups. Subjects who are considered bDMARD-inadequate responders (lack of efficacy), as determined by the Investigator, are not eligible.

Rescue therapy will be offered to subjects who meet the following criteria:

Placebo:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ABT-494 treatment.
- At Week 26, all remaining subjects will be switched to blinded ABT-494 treatment regardless of clinical response.

Methodology (Continued):

ADA:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ABT-494 treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ABT-494 treatment.

ABT-494:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ADA treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ADA treatment.

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1. Another unblinded analysis may be conducted for regulatory purposes after all subjects have completed Period 1 (Week 48).

Each subject will undergo a maximum of 4 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation; in addition, all subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14.

Subjects who complete the Week 48 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (up to 5 years). Subjects will continue study treatment as assigned in Period 1. Subjects who are assigned to the ABT-494 15 mg QD treatment group at the end of Period 1 will continue to receive ABT-494 15 mg QD in a blinded manner. Subjects who are assigned to adalimumab 40 mg eow at the end of Period 1 will continue to receive adalimumab 40 mg eow in a blinded manner. When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Each subject will undergo an x-ray examination of bilateral hands and feet at Week 96/Premature Discontinuation (unless repeat testing is needed due to failure to meet the quality requirements) and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous [redacted] weeks.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, at least 18 years old.
2. Diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 12.5 mg/week) for ≥ 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation.

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

Main Inclusion:

4. Subject meets both of the following disease activity criteria:
   c. ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
   d. hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at Screening Visit.
5. Subject has at least one of the following at Screening:
   d. ≥ 3 bone erosions on x-ray; or
   e. ≥ 1 bone erosion and a positive rheumatoid factor; or
   f. ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody.
6. Subjects with prior exposure to only one bDMARD (except ADA) may be enrolled (up to 20% of total study population). Specifically, prior to enrollment:
   a. Patients with limited exposure to a bDMARD (< 3 months), OR
   b. Patients who are responding to a bDMARD but had to discontinue due to intolerability (regardless of treatment duration).
7. Except for MTX, subject must have discontinued all csDMARDs. The washout period for csDMARDs prior to the first dose of study is specified below or should be at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
   - ≥ 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).

Main Exclusion:

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Subjects who have had any exposure to adalimumab or subjects who have been treated with other bDMARD therapy for ≥ 3 months who are considered inadequate responders (lack of efficacy) to bDMARD therapy as determined by the Investigator.
3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms], or any arthritis with onset prior to age 17 years). History of secondary Sjogren's Syndrome is permitted.
4. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase > 2 × ULN; serum alanine transaminase > 2 × ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73m^2; total white blood cell count < 2,500/μL; absolute neutrophil count < 1,500/μL; platelet count < 100,000/μL; absolute lymphocyte count < 800/μL; and hemoglobin < 10 g/dL.

Investigational Product:	ABT-494
Dose:	15 mg QD
Mode of Administration:	Oral
Reference Therapy:	ADA, matching placebo for ADA, matching placebo for ABT-494
Dose:	ADA 40 mg eow, matching placebo for ABT-494 QD, and matching placebo for ADA eow
Mode of Administration:	ADA and matching placebo for ADA will be administered by subcutaneous injection eow and ABT-494 and matching placebo will be given orally QD
Duration of Treatment:	Period 1: 48 weeks; Period 2: up to 5 years

Criteria for Evaluation:

Efficacy:

Period 1

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response at Week 12 (US/FDA regulatory purposes) or the proportion of subjects achieving clinical remission (CR) based on Disease Activity Score (DAS)28 (C-reactive protein [CRP]) at Week 12 (EU/EMA regulatory purposes).

ACR20 response rate will be determined based on 20% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain (Visual Analog Scale [VAS]), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI), or hsCRP.

CR is defined as DAS28 (CRP) < 2.6.

Key secondary endpoints (ABT-494 versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

1. Change from baseline in Disease Activity Score (DAS)28 (C-reactive protein [CRP]) at Week 12;
2. Change from baseline in mTSS at Week 26;
3. Change from baseline in HAQ-DI at Week 12;
4. ACR50 response rate at Week 12 (non-inferiority of ABT-494 versus ADA);
5. Change from baseline in Short Form 36 (SF-36) Physical Component Score (PCS) at Week 12;
6. Proportion of subjects achieving low disease activity (LDA) based on DAS28 [CRP] ≤ 3.2 at Week 12;
7. Proportion of subjects achieving clinical remission (CR) based on DAS28 (CRP) at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12;
9. Change from baseline in morning stiffness at Week 12;
10. Change from baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) at Week 12;
11. ACR50 response rate at Week 12 (superiority of ABT-494 vs. ADA);
12. Change from baseline in Patient's Assessment of Pain at Week 12 (superiority of ABT-494 vs. ADA);
13. Change from baseline in HAQ-DI at Week 12 (superiority of ABT-494 vs. ADA).

Criteria for Evaluation (Continued):

Efficacy (Continued):

Key secondary endpoints (ABT-494 versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

1. The change from baseline in modified Total Sharp Score (mTSS) at Week 26;
2. Proportion of subjects achieving LDA based on DAS28 [CRP] ≤ 3.2 at Week 12;
3. Change from baseline in DAS28 (CRP) at Week 12;
4. Change from baseline in HAQ-DI at Week 12;
5. ACR20 response rate at Week 12;
6. ACR50 response rate at Week 12;
7. ACR70 response rate at Week 12;
8. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of ABT-494 versus ADA);
9. Change from baseline in SF-36 PCS at Week 12;
10. Change from baseline in FACIT-F at Week 12;
11. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26;
12. Change from baseline in RA-WIS at Week 12;
13. Change from baseline in morning stiffness at Week 12.

Additional endpoints are:

- Change from baseline in individual components of ACR response at all visits;
- ACR20/50/70 response rates at all visits;
- Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]) at all visits;
- Change from baseline in CDAI and SDAI at all visits;
- Proportions of subjects achieving LDA or CR based on DAS28 (CRP) and DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria at all visits (see below);
- Change from baseline in EQ-5D-5L, SF-36, FACIT-F and RA-WIS at Weeks 12, 26, and 48;
- Change from baseline in modified Total Sharp Score (mTSS) at Weeks 26 and 48;
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Weeks 26 and 48;
- Change from baseline in joint space narrowing score and joint erosion score at Weeks 26 and 48;
- Change from baseline in morning stiffness at all visits;
- Proportion of subjects achieving MCID in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3) at all visits;
- ACR/EULAR Boolean remission at all visits.

Criteria for Evaluation (Continued):

Efficacy (Continued):

	DAS28 (CRP) and DAS28 (ESR)	SDAI	CDAI
LDA	≤ 3.2	≤ 11.0	≤ 10
CR	< 2.6	≤ 3.3	≤ 2.8

Period 2

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 60, 72, 84, 96, and every 12 weeks thereafter until completion of the study:

- ACR20/50/70 response rates;
- Change from baseline in individual ACR components;
- Change from baseline in DAS28 (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in morning stiffness;
- Proportion of subjects achieving LDA and the proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria (as defined for Period 1);
- Concomitant corticosteroid use (systemic use and intra-articular injections);
- ACR/EULAR Boolean remission.

Additionally, assessment for the evaluation of radiographic changes in Period 2 will occur at Week 96 and every 96 weeks thereafter (or Premature Discontinuation visit):

- Change from baseline in modified Total Sharp Score (mTSS);
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS of ≤ 0);
- Change from baseline in Radiographic joint space narrowing and erosion scores.

Pharmacokinetic (Period 1 Only):

Blood samples for assay of ABT-494 and possibly other medications in plasma will be collected at Weeks 2, 4, 8, 12, 14, 18, 22, 26, 30, 36, 42, and 48/Premature Discontinuation.

Exploratory Research Variables and Validation Studies (Optional) (Period 1 Only):

Prognostic, predictive, and pharmacodynamics biomarkers signatures may be evaluated. Samples for pharmacogenetic, epigenetic, transcriptomic, and proteomic and targeted protein investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites, or lipids.

Safety:

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

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.

Period 1 Efficacy

Analysis of the Primary and Key Secondary Endpoints:

All statistical comparisons of ABT-494 versus comparators for the primary and key secondary endpoints will be conducted using a two-sided alpha = 0.05 level of significance.

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 meets the requirements of significance.

For binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparisons between ABT-494 and placebo will be conducted using the Cochran-Mantel-Haenszel test adjusting for main stratification factors. For LDA response rates at Week 12, analysis will be conducted to test the non-inferiority of ABT-494 versus ADA using the 95% confidence interval of treatment difference against a non-inferiority margin of 10%. For ACR50 response rate at Week 12, similar analysis of non-inferiority will be conducted for US/FDA purposes. Superiority of ABT-494 vs ADA will also be tested for LDA and ACR50.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between ABT-494 and placebo will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates. For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of ABT-494 vs adalimumab will also be tested for US/FDA purposes.

For mTSS-based endpoints, both linear extrapolation and As Observed (AO) analyses will be conducted. For all other endpoints, non-responder imputation approach will serve as the primary analysis approach for binary endpoints and multiple imputation will serve as the primary analysis approach for key continuous endpoints. Sensitivity analyses based on observed cases approach will also be conducted for key endpoints.

Long-Term Efficacy for Period 1 and Period 2 Combined

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

Pharmacokinetic:

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 ABT-494 oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

Statistical Methods (Continued): **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. Analyses will be conducted for Period 1 alone, as well as for Period 1 and Period 2 combined. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from baseline to defined time points will be tabulated.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M14-465
Name of Study Drug: Upadacitinib	**Phase of Development:** 3
Name of Active Ingredient: Upadacitinib	**Date of Protocol Synopsis:** 01 December 2017
Protocol Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)	
Objectives: **Period 1** 4. To compare the efficacy of upadacitinib 15 mg once daily (QD) versus placebo, and versus adalimumab (ADA) for the treatment of signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA who are on a stable background of methotrexate (MTX) and who have an inadequate response to MTX (MTX-IR). 5. To compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR). 6. To compare the safety and tolerability of upadacitinib 15 mg QD versus placebo, and versus ADA in subjects with moderately to severely active RA subjects who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR). **Period 2** To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	
Investigators: Multicenter	
Study Sites: Approximately 400	

Study Population: Adult female and male subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP) ≥ 5 mg/L (central lab, upper limit of normal [ULN] 2.87 mg/L) at Screening. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week).
Number of Subjects to be Enrolled: Approximately 1500

Methodology:

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of upadacitinib 15 mg QD versus placebo and versus ADA for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of MTX and have an inadequate response to MTX (MTX-IR). Period 1 is also designed to compare the efficacy of upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

The study duration will include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes the last visit of the double-blind treatment period) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: Upadacitinib (ABT-494) 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg every other week [eow]) (N = 300)

Subjects will receive both oral study drug QD (either upadacitinib 15 mg or matching placebo) and subcutaneous study drug eow (either ADA 40 mg or matching placebo) until the study is unblinded.

Subjects must have been on oral or parenteral MTX therapy for ≥ 3 months, on a stable MTX dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week), and must remain on a stable dose throughout the study; the MTX dose may be decreased only for safety reasons. In addition, all subjects should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Starting at the Week 26 visit (after Week 26 assessments have been performed), initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, is allowed as per local label. Starting at Week 48 (after Week 48 assessments have been performed) and thereafter, initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide).

Subjects with prior exposure to at most one biologic disease-modifying anti-rheumatic drug (bDMARD) (except ADA) for RA may be enrolled in the study (up to 20% of total number of subjects) after the required washout period is satisfied and if they have a) limited bDMARD exposure (< 3 months), OR b) response to a bDMARD but had to discontinue that bDMARD due to intolerability (regardless of treatment duration). These subjects will be equally stratified across all treatment groups. Subjects who are considered bDMARD-inadequate responders (lack of efficacy), as determined by the Investigator, are not eligible.

Rescue therapy will be offered to subjects who meet the following criteria:

Methodology (Continued):

Placebo:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects will be switched to blinded upadacitinib treatment regardless of clinical response.

ADA:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded upadacitinib treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded upadacitinib treatment.

Upadacitinib:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ADA treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ADA treatment.

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

Each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation. Subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14; in addition, subjects who prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint.

Subjects who complete the Week 48 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (up to 5 years). Subjects will continue study treatment as assigned in Period 1. Subjects who are assigned to the upadacitinib 15 mg QD treatment group at the end of Period 1 will continue to receive upadacitinib 15 mg QD in a blinded manner. Subjects who are assigned to adalimumab 40 mg eow at the end of Period 1 will continue to receive adalimumab 40 mg eow in a blinded manner. When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Each subject will undergo an x-ray examination of bilateral hands and feet at Week 96/Premature Discontinuation (unless repeat testing is needed due to failure to meet the quality requirements) and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous [redacted] weeks.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, at least 18 years old.
2. Diagnosis of RA for ≥ 3 months who fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 12.5 mg/week) for ≥ 4 weeks prior to the first dose of study drug. In addition, all subjects should take a dietary supplement of folic acid or folinic acid throughout the study participation.
4. Subject meets both of the following disease activity criteria:
   e. ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
   f. hsCRP ≥ 5 mg/L (central lab, ULN 2.87 mg/L) at Screening Visit.
5. Subject has at least one of the following at Screening:
   g. ≥ 3 bone erosions on x-ray; or
   h. ≥ 1 bone erosion and a positive rheumatoid factor; or
   i. ≥ 1 bone erosion and a positive anti-cyclic citrullinated peptide autoantibody.
6. Subjects with prior exposure to only one bDMARD (except ADA) may be enrolled (up to 20% of total study population). Specifically, prior to enrollment:
   a. Patients with limited exposure to a bDMARD (< 3 months), OR
   b. Patients who are responding to a bDMARD but had to discontinue due to intolerability (regardless of treatment duration).
7. Except for MTX, subject must have discontinued all csDMARDs. The washout period for csDMARDs prior to the first dose of study is specified below or should be at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
   - ≥ 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).

Main Exclusion: 1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib). 2. Subjects who have had any exposure to adalimumab or subjects who have been treated with other bDMARD therapy for ≥ 3 months who are considered inadequate responders (lack of efficacy) to bDMARD therapy as determined by the Investigator. 3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms], or any arthritis with onset prior to age 17 years). History of secondary Sjogren's Syndrome is permitted. 4. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase > 2 × ULN; serum alanine transaminase > 2 × ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73m^2; total white blood cell count < 2,500/μL; absolute neutrophil count < 1,500/μL; platelet count < 100,000/μL; absolute lymphocyte count < 800/μL; and hemoglobin < 10 g/dL.	
Investigational Product:	Upadacitinib
Dose:	15 mg QD
Mode of Administration:	Oral
Reference Therapy:	ADA, matching placebo for ADA, matching placebo for upadacitinib
Dose:	ADA 40 mg eow, matching placebo for upadacitinib QD, and matching placebo for ADA eow
Mode of Administration:	ADA and matching placebo for ADA will be administered by subcutaneous injection eow and upadacitinib and matching placebo will be given orally QD
Duration of Treatment: Period 1: 48 weeks; Period 2: up to 5 years	

Criteria for Evaluation:

Efficacy:

Period 1

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response at Week 12 (US/FDA regulatory purposes) or the proportion of subjects achieving clinical remission (CR) based on Disease Activity Score (DAS)28 (C-reactive protein [CRP]) at Week 12 (EU/EMA regulatory purposes).

ACR20 response rate will be determined based on 20% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain (Visual Analog Scale [VAS]), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI), or hsCRP.

CR is defined as DAS28 (CRP) < 2.6.

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

1. Change from baseline in Disease Activity Score (DAS)28 (C-reactive protein [CRP]) at Week 12;
2. Change from baseline in mTSS at Week 26;
3. Change from baseline in HAQ-DI at Week 12;
4. ACR50 response rate at Week 12 (non-inferiority of upadacitinib versus ADA);
5. Change from baseline in Short Form 36 (SF-36) Physical Component Score (PCS) at Week 12;
6. Proportion of subjects achieving low disease activity (LDA) based on DAS28 [CRP] ≤ 3.2 at Week 12;
7. Proportion of subjects achieving clinical remission (CR) based on DAS28 (CRP) at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12;
9. Change from baseline in morning stiffness at Week 12;
10. Change from baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) at Week 12;
11. ACR50 response rate at Week 12 (superiority of upadacitinib vs. ADA);
12. Change from baseline in Patient's Assessment of Pain at Week 12 (superiority of upadacitinib vs. ADA);
13. Change from baseline in HAQ-DI at Week 12 (superiority of upadacitinib vs. ADA).

Criteria for Evaluation (Continued):

Efficacy (Continued):

Other key secondary endpoints (upadacitinib versus placebo) for US/FDA regulatory purposes are:

- ACR50 response rate at Week 12
- ACR70 response rate at Week 12
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

1. The change from baseline in modified Total Sharp Score (mTSS) at Week 26;
2. Proportion of subjects achieving LDA based on DAS28 [CRP] ≤ 3.2 at Week 12;
3. Change from baseline in DAS28 (CRP) at Week 12;
4. Change from baseline in HAQ-DI at Week 12;
5. ACR20 response rate at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of upadacitinib versus ADA);
7. Change from baseline in SF-36 PCS at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12
9. Change from baseline in morning stiffness at Week 12.
10. Change from baseline in FACIT-F at Week 12
11. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26;

Other key secondary endpoints (upadacitinib versus placebo) for EU/EMA regulatory purposes are:

1. ACR50 response rate at Week 12
2. ACR70 response rate at Week 12

Criteria for Evaluation (Continued):

Efficacy (Continued):

Additional endpoints (upadacitinib versus placebo and adalimumab) are:

- Change from baseline in individual components of ACR response at all visits;
- ACR20/50/70 response rates at all visits;
- Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]) at all visits;
- Change from baseline in CDAI and SDAI at all visits;
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP) and DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria at all visits (see below);
- Change from baseline in morning stiffness at all visits;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22 at all visits;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 at all visits;
- ACR/EULAR Boolean remission at all visits;
- Change from baseline in EQ-5D-5L, SF-36, FACIT-F and RA-WIS at Weeks 12, 26, and 48;
- Change from baseline in modified Total Sharp Score (mTSS) at Weeks 26 and 48;
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Weeks 26 and 48;
- Change from baseline in joint space narrowing score and joint erosion score at Weeks 26 and 48

Criteria for Evaluation (Continued):

Efficacy (Continued):

	DAS28 (CRP) and DAS28 (ESR)	SDAI	CDAI
LDA	≤ 3.2	≤ 11.0	≤ 10
CR	< 2.6	≤ 3.3	≤ 2.8

Period 2

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 60, 72, 84, 96, and every 12 weeks thereafter until completion of the study:

- ACR20/50/70 response rates;
- Change from baseline in individual ACR components;
- Change from baseline in DAS28 (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in CDAI and SDAI;
- Change from baseline in morning stiffness;
- Proportion of subjects achieving LDA and the proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria (as defined for Period 1);
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.22;
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3;
- Concomitant corticosteroid use (systemic use and intra-articular injections);
- ACR/EULAR Boolean remission.

Additionally, assessment for the evaluation of radiographic changes in Period 2 will occur at Week 96 and every 96 weeks thereafter (or Premature Discontinuation visit):

- Change from baseline in modified Total Sharp Score (mTSS);
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS of ≤ 0);
- Change from baseline in Radiographic joint space narrowing and erosion scores.

Pharmacokinetic (Period 1 Only):

Blood samples for assay of upadacitinib and possibly other medications in plasma will be collected at Weeks 2, 4, 8, 12, 14, 18, 22, 26, 30, 36, 42, and 48/Premature Discontinuation.

Exploratory Research Variables and Validation Studies (Optional) (Period 1 Only):

Prognostic, predictive, and pharmacodynamics biomarkers signatures may be evaluated. Samples for pharmacogenetic, epigenetic, transcriptomic, and proteomic and targeted protein investigations will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites, or lipids.

Safety:

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

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.

Period 1 Efficacy

Analysis of the Primary and Key Secondary Endpoints:

All statistical comparisons of upadacitinib versus comparators for the primary and key secondary endpoints will be conducted using a two-sided alpha = 0.05 level of significance.

In order to preserve Type I error, a step-down approach will be used to test the primary and ranked key secondary endpoints where statistical significance can be claimed for a lower ranked endpoint only if the previous endpoints in the sequence meets the requirements of significance.

For binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparisons between upadacitinib and placebo will be conducted using the Cochran-Mantel-Haenszel test adjusting for main stratification factors. For LDA response rates at Week 12, analysis will be conducted to test the non-inferiority of upadacitinib versus ADA using the 95% confidence interval of treatment difference against a non-inferiority margin of 10%. For ACR50 response rate at Week 12, similar analysis of non-inferiority will be conducted for US/FDA purposes. Superiority of upadacitinib vs ADA will also be tested for LDA and ACR50.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between upadacitinib and placebo will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates. For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of upadacitinib vs adalimumab will also be tested.

For mTSS-based endpoints, both linear extrapolation and As Observed (AO) analyses will be conducted. For all other endpoints, non-responder imputation approach will serve as the primary analysis approach for key binary endpoints and multiple imputation will serve as the primary analysis approach for key continuous endpoints. Sensitivity analyses based on observed cases approach will also be conducted for key endpoints.

Long-Term Efficacy for Period 1 and Period 2 Combined

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

Pharmacokinetic:

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.

Statistical Methods (Continued):

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. Analyses will be conducted for both short term and long term. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from baseline to defined time points will be tabulated.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add: MCID

MCID	minimum clinically important differences

Section 5.1 Overall Study Design and Plan: Description
Third paragraph previously read:

The study duration will include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes Week 48 the last visit of the double-blind treatment period) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Has been changed to read:

The study duration will include a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes Period 1) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Section 5.1 Overall Study Design and Plan: Description
Sixth paragraph, fourth sentence previously read:

Starting at the Week 26 visit (after Week 26 assessments have been performed), initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label.

Has been changed to read:

Starting at the Week 26 visit (after Week 26 assessments have been performed) and thereafter, initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol is allowed as per local label. Starting at Week 48 (after Week 48 assessments have been performed) and thereafter, initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide).

Section 5.1 Overall Study Design and Plan: Description
Add: new seventh paragraph

Starting at the Week 48 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) (see Section 5.4.1) must be discontinued from study drug.

Section 5.1 Overall Study Design and Plan: Description
Ninth paragraph previously read:

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of

Period 1. Another unblinded analysis may be conducted for regulatory purposes after all subjects have completed Period 1 (Week 48).

Has been changed to read:

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

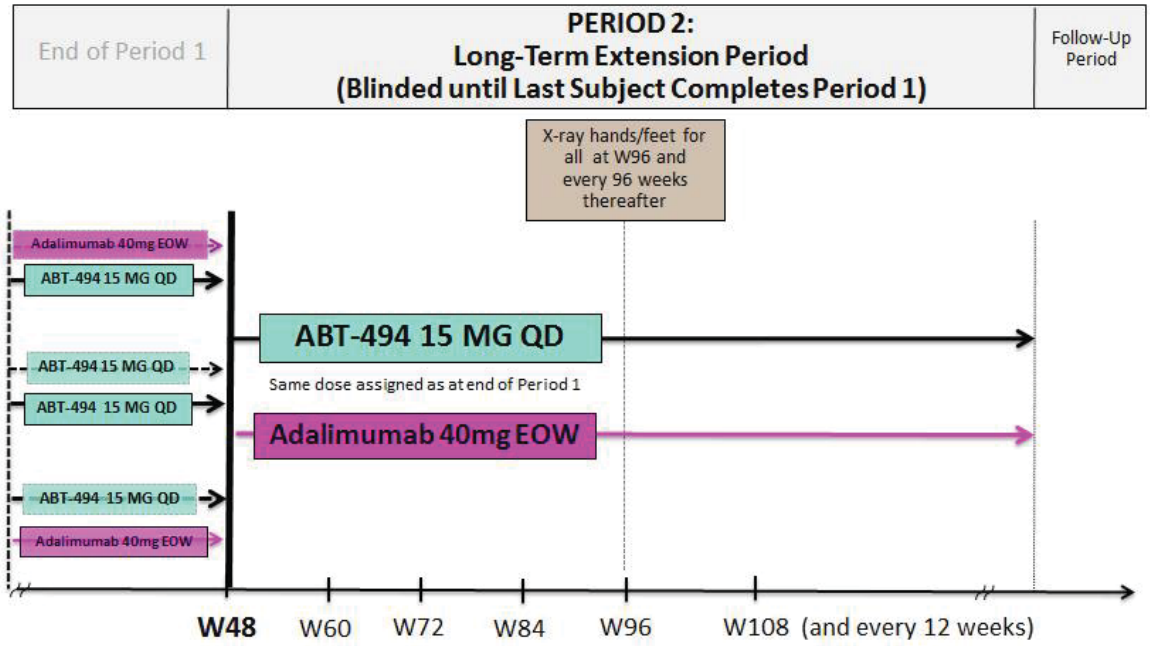
Overall Study Design and Plan: Description
Tenth paragraph previously read:

Each subject will undergo a maximum of 4 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation; in addition, all subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14 (refer to Section 5.3.1.1 for additional details).

Has been changed to read:

Each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation. Subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14; in addition, subjects who prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint (refer to Section 5.3.1.1 for additional details).

Figure 1. Period 1 Study Design
Previously read:



BL = baseline; EOW = every other week; MTX = methotrexate; QD = once daily; RA = rheumatoid arthritis; SJC = swollen joint count; TJC = tender joint count; W = week

At W26, all placebo patients will be switched to ABT-494 15 mg regardless of response.

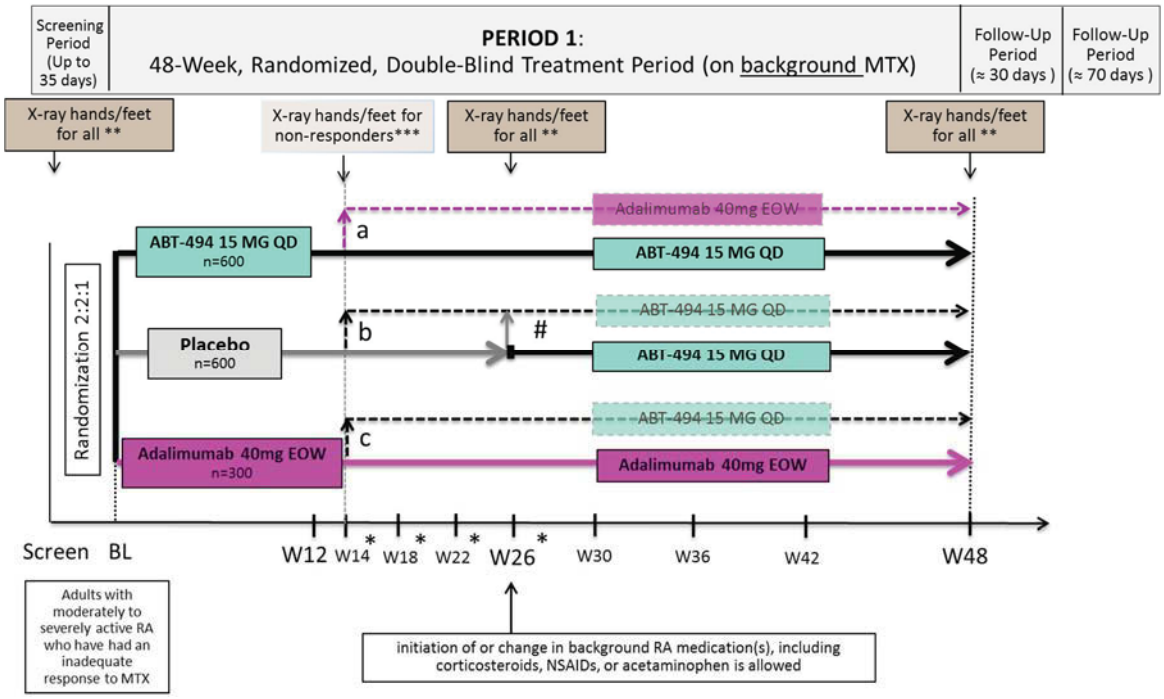
** All patients will receive x-rays of hands and feet at Screening, W26, and W48.

*** X-rays at W14 will only be performed for non-responders, see Section 5.3.1.1.

Notes: The follow-up period is only for subjects who do not enter Period 2.

Early escape for non-responders: (a) from ABT-494 15 mg QD to adalimumab at W14, W18, W22, or W26; (b) from placebo to ABT-494 15 mg QD at W14, W18, or W22; (c) from adalimumab to ABT-494 15 mg QD at W14, W18, W22, or W26. Non-response at W14, W18, or W22 is defined as not achieving ≥ 20% improvement in TJC and SJC compared to baseline. Non-response at W26 is defined as not achieving LDA according to CDAI (LDA defined as CDAI ≤ 10). For more details regarding x-rays of hands and feet, see Section 5.3.1.1.

Has been changed to read:



BL = baseline; EOW = every other week; MTX = methotrexate; QD = once daily; RA = rheumatoid arthritis; SJC = swollen joint count; TJC = tender joint count; W = week

\# At W26, all placebo patients will be switched to upadacitinib 15 mg regardless of response.

** All patients will receive x-rays of hands and feet at Screening, W26, and W48.

*** X-rays at W14 will only be performed for non-responders, see Section 5.3.1.1.

Notes: The follow-up period is only for subjects who do not enter Period 2.

Early escape for non-responders: (a) from upadacitinib 15 mg QD to adalimumab at W14, W18, W22, or W26; (b) from placebo to upadacitinib 15 mg QD at W14, W18, or W22; (c) from adalimumab to upadacitinib 15 mg QD at W14, W18, W22, or W26. Non-response at W14, W18, or W22 is defined as not achieving ≥ 20% improvement in TJC and SJC compared to baseline. Non-response at W26 is defined as not achieving LDA according to CDAI (LDA defined as CDAI ≤ 10). For more details regarding x-rays of hands and feet, see Section 5.3.1.1.

Section 5.1 Overall Study Design and Plan: Description
Subsection Period 2 (Long-Term Extension Period [up to 5 years])
Last sentence previously read:

Starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits (see Section 5.4.1 will be discontinued from study drug treatment.

Has been changed to read:

Starting at Week 48 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) (see Section 5.4.1) must be discontinued from study drug.

Section 5.1 Overall Study Design and Plan: Description
Subsection Discontinuation of Study Drug and Continuation of Study Participation (Period 1 and Period 2)
Add: new last sentence

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.

Section 5.1 Overall Study Design and Plan: Description
Subsection Premature Discontinuation of Study (Withdrawal of Informed Consent) (Period 1 and Period 2)
Third sentence previously read:

In addition, if the subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Has been changed to read:

In addition, a 30-day follow-up visit (or phone call if a visit is not possible) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Section 5.1 Overall Study Design and Plan: Description
Subsection Premature Discontinuation of Study (Withdrawal of Informed Consent) (Period 1 and Period 2)
Add: new last sentence

The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

Section 5.1 Overall Study Design and Plan: Description
Subsection Follow-Up Period
Third paragraph previously read:

A follow-up phone call will also occur 70 days after the last administration of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Has been changed to read:

A follow-up phone call will also occur 70 days after the last administration of subcutaneous study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

The 30 day follow-up visit and 70 day follow-up call are not required for subjects who discontinued study drug and continued study participation with completion of at least one study visit approximately 30 days after last dose of oral or 70 days after last dose of subcutaneous study drug, respectively.

Section 5.2.3 Prior, Concomitant, and Prohibited Therapy
Last paragraph previously read:

The AbbVie Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

Has been changed to read:

The AbbVie Therapeutic Area Medical Director identified in Section 6.1.5 *(Serious Adverse event Reporting)* should be contacted if there are any questions regarding concomitant or prior therapies.

Section 5.2.3.1 Permitted Background RA Therapy
Last paragraph previously read:

Starting at Week 26 (after Week 26 assessments have been performed) and thereafter, initiation of or change in corticosteroids, NSAIDs, acetaminophen/paracetamol, or adding or increasing doses of csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 9, Section 5.2.1) is allowed as per local label. For RA flare treatment, no more than 3 consecutive days of high-dose systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Has been changed to read:

Starting at Week 26 (after Week 26 assessments have been performed) and thereafter, initiation of or change in corticosteroids, NSAIDs, acetaminophen/paracetamol is allowed as per local label. For RA flare treatment, no more than 3 consecutive days of systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Starting at Week 48 (after Week 48 assessments have been performed) and thereafter initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 9, Section 5.2.1).

Section 5.2.3.2 Prohibited Therapy
Subsection Corticosteroids
First sentence previously read:

Oral corticosteroids > 10 mg prednisone/day or equivalent are NOT allowed in Period 1.

Has been changed to read:

Oral corticosteroids > 10 mg prednisone/day or equivalent are NOT allowed up to Week 26.

Table 1. Examples of Commonly Used Strong CYP3A Inhibitors and Inducers
Column "Strong CYP3A Inducers"
Add: Rifapentine

Rifapentine

Section 5.2.3.2 Prohibited Therapy
Subsection Vaccines
First paragraph previously read:

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) 4 weeks before first dose of study drug with appropriate precautions or administered at least 30 days after last dose of oral study drug, or at least 70 days after last dose of subcutaneous study drug.

Has been changed to read:

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap). It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks before first dose of study drug or administered at least 30 days after last dose of oral study drug, or at least

70 days after the last dose of subcutaneous study drug. If the herpes zoster vaccine is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing immunity to varicella should be confirmed with antibody testing at or prior to screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative the herpes zoster vaccine should not be administered.

If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) 4 weeks before first dose of study drug with appropriate precautions or administered at least 30 days after last dose of oral study drug, or at least 70 days after last dose of subcutaneous study drug.

Section 5.2.3.2 Prohibited Therapy
Subsection <u>Traditional Chinese Medicine</u>
Previously read:

Traditional Chinese medicine (oral) 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.

Has been changed to read:

Traditional oral Chinese medicine is not permitted during the study as these may interfere with upadacitinib metabolism and exposure and may impact efficacy and safety of upadacitinib treatment. Subjects must have discontinued traditional Chinese medicine at least 4 weeks prior to the first dose of study drug.

Section 5.2.4 Contraception Recommendations
Subsection <u>Contraception Recommendation for Females</u>
Third and fourth paragraph previously read:

If the female subject is < 55 years of age:

AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.

Has been changed to read:

If the female subject is < 55 years of age and is not permanently surgically sterile, as defined above, and has had no menses for ≥ 12 months FSH should be tested at Screening.

Section 5.2.4 Contraception Recommendations
Subsection Contraception Recommendation for Females
Add: new eighth paragraph

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

Section 5.2.4 Contraception Recommendations
Subsection Contraception Recommendation for Males
Add: new first paragraph

Based on data from animal studies (including a fertility study) there is no effect of upadacitinib on male reproduction.

Section 5.2.4 Contraception Recommendations
Subsection Contraception Recommendation for Males
First paragraph previously read:

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

Has been changed to read:

For a male subject who is surgically sterile (vasectomy with medical assessment confirming surgical success) OR has a female partner who is postmenopausal or permanently sterile, no contraception is required.

Section 5.2.4 Contraception Recommendations
Subsection <u>Contraception Recommendation for Males</u>
Second bullet previously read:

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

Has been changed to read:

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

Table 2. Study Activities (Period 1)
Activity "Prior/concomitant therapy, "Latent TB risk assessment form[i]" previously read:

Activity	Screening D–35 to D–1	BL D1[b]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/ PD[a] D337	30-Day F/U Visit/ Call[c]	70-Day F/U Call[c]
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X[g]	X	X	X	X	X	
Latent TB risk assessment form[i]	X													X		

Has been changed to read:

Activity	Screening D–35 to D–1	BL D1[b]	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 D85	Wk 14 D99	Wk 18 D127	Wk 22 D155	Wk 26 D183	Wk 30 D211	Wk 36 D253	Wk 42 D295	Wk 48/ PD[a] D337	30-Day F/U Visit/ Call[c]	70-Day F/U Call[c]
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	
Latent TB risk assessment form[i]	X													X[i]		

Table 2. Study Activities (Period 1)
Table note "c."
Add: new last sentence

The 70 day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

Table 2. Study Activities (Period 1)
Table note "g.," "i.," "j.," "l.," "s.," and "aa." previously read:

g. At Week 26 (after Week 26 assessments have been performed), per Investigator judgment, may add csDMARDs (concomitant use of up to 2 csDMARDs, except the combination of MTX and leflunomide, or increasing csDMARD dose).

i. Refer to Section 5.3.1.1. Study Procedures TB Testing for specific requirements for TB testing and TB Prophylaxis.

j. The screening chest x-ray will not be required if a subject had a previous normal chest-x-ray within 90 days of Screening, provided that all source documentation is available at the site (refer to Section 5.3.1.1 Chest X-Ray for specific requirements). At Week 48, 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.

l. For subjects who do not enter Period 2 or prematurely discontinue from the study, an ECG will be performed.

s. hsCRP results will remain blinded to the Sponsor, Investigator, study site personnel, and the subject for all visits except Screening.

aa. Starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

Has been changed to read:

g. At Week 48 (after Week 48 assessments have been performed), per Investigator judgment, may add or change csDMARDs (concomitant use of up to 2 csDMARDs, except the combination of MTX and leflunomide, or increasing csDMARD dose).

i. Complete the latent TB risk assessment form annually. Refer to Section 5.3.1.1. Study Procedures TB Testing for specific requirements for TB testing and TB Prophylaxis.

j. The screening chest x-ray will not be required if a subject had a previous normal chest-x-ray within 90 days of Screening, provided that all source documentation is available at the site (refer to Section 5.3.1.1 Chest X-Ray for specific requirements). At Week 48, obtain chest x-ray for subjects with newly identified TB risk factors based on the TB risk assessment form, or 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.

l. .All subjects will have an ECG at Week 48 and PD visit as applicable.

s. Central lab hsCRP results will remain blinded to the Sponsor, Investigator, study site personnel, and the subject for all visits except Screening. 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. Any local hsCRP or local CRP tests should not be reported to the investigator until treatment allocation is unblinded.

aa. Starting at Week 48, subjects who failed to show at least 20% improvement in both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

Table 4. Study Activities (Period 2)
Table note "d.," "e.," "f.," and "l." previously read:

d. TB testing should be performed every 48 weeks after Week 96 in subjects with previous negative Quantiferon and/or PPD tests. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines. Refer to Section 5.3.1.1, Study Procedures, TB Testing for specific requirements for TB testing and TB Prophylaxis. Study drug(s) should not be withheld at the time of the first positive TB test.
e. Obtain chest x-ray every 48 weeks after Week 96 for subjects with TB risk factors as identified by the TB risk assessment form, or 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.
f. For subjects in the Czech Republic, ECGs will be performed every 48 weeks after Week 96. An ECG may be performed at any visit if deemed necessary by the Investigator.
l. hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject for all visits until the last subject reaches the end of Period 1.

Has been changed to read:

d. TB testing should be performed every 48 weeks after Week 96 in subjects with previous negative QuantiFERON-TB Gold and/or PPD tests. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines. Refer to Section 5.3.1.1, Study Procedures, TB Testing for specific requirements for TB testing and TB Prophylaxis. Study drug(s) should not be withheld at the time of the first positive TB test.
e. Obtain chest x-ray every 48 weeks after Week 96 for subjects with newly identified TB risk factors based on the TB risk assessment form, or 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.
f. ECGs will be performed every 48 weeks after Week 48. An ECG may be performed at any visit if deemed necessary by the Investigator.
l. hsCRP results will remain blinded to Sponsor, Investigator and study site personnel, and the subject for all visits until the last subject reaches the end of Period 1.

Section 5.3.1.1 Study Procedures
Subsection <u>TB Testing/TB Prophylaxis</u>
Previously read:

Period 1

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.

All subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix F) and tested for TB infection by QuantiFERON-TB Gold test. 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 site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF.

- Preferred Method: QuantiFERON-TB Gold Test will be analyzed by the central laboratory (QuantiFERON test is preferred over PPD skin test).
- If QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD Skin Test are required per local guidelines): the PPD Skin Test (also known as a TB Skin Test) will be performed according to standard clinical practice. The TB Skin Test 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 for RA subjects is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.

If a subject had a negative QuantiFERON-TB Gold (and/or PPD) test (or IGRA equivalent such as T-SPOT TB test) 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 Therapeutic Area Medical Director. The results of the TB test(s) will be retained at the site as the original source documentation.

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 who reside 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 chest x-ray 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 chest x-ray not suggestive of active TB need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie Therapeutic Area Medical Director 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.

In the event both a PPD test and a QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test, unless otherwise required by local guidelines. If the QuantiFERON-TB Gold test is indeterminate, the site should repeat the test with another blood sample. If the second QuantiFERON-TB Gold test is also indeterminate, the subject is considered to be positive.

At a site with capacity to perform both tests, if a PPD is placed as the only form of TB test 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 alone or other IGRA (negative result), then the subject should have their annual TB test performed with the Quantiferon-TB Gold Test.

Subjects with a negative QuantiFERON®-TB Gold test (and/or negative PPD TB skin test) and chest x-ray (CXR) not suggestive of active TB or prior TB exposure may be enrolled.

If the subject has evidence of a latent TB infection (QuantiFERON®-TB Gold test and/or the PPD test positive and the subject has a CXR not suggestive of active TB), prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). The prophylaxis needs to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug. If the Investigator deems that it is necessary, consultation with a TB expert could be considered.

Of Note: Rifampicin is 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 within 1 year prior to first study drug administration will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

Subjects with a documented completion of a full course of anti-TB therapy greater than 1 year prior to first study drug administration may be allowed to enter the study only after consultation with the AbbVie Therapeutic Area Medical Director.

Newly initiated prophylactic treatment should be captured in the eCRF and in the source documents. Prior therapy should be captured in the eCRF.

Period 2

For subjects with a negative QuantiFERON-TB Gold (and/or PPD) test at Screening, an annual QuantiFERON-TB Gold (and/or PPD) re-test will be performed (or both if required by local guidelines). If one of the annual tests has a positive test result (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Expert consultation can be considered per Investigator's discretion. Any positive TB screen after the patient has started the study, should be reported as an adverse event (AE).

Obtain a CXR annually for subjects with TB risk factors as identified by the TB risk assessment form (Appendix F) or for subjects living in areas endemic for TB or for subjects with newly positive PPD or QuantiFERON-TB Gold test.

Subjects with new evidence of latent TB during the study should initiate prophylactic treatment immediately per local guidelines. Study drug(s) should not be withheld and Isoniazid should be initiated and 2 to 4 weeks later (per local guidelines), subject should be re-evaluated (unscheduled visit) for signs and symptoms and isoniazid toxicity.

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 Therapeutic Area Medical Director.

Has been changed to read:

The TB screening tests provide 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 F) and tested for TB infection by QuantiFERON-TB Gold test. 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 site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF. The TB risk assessment form will be completed annually for all subjects, regardless of TB test results.

If a subject had a negative PPD 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. These cases may be discussed with the AbbVie TA MD. The results of the TB test(s) will be retained at the site as the original source documentation.

Subjects with a negative TB test and chest x-ray (CXR) not suggestive of active TB or prior TB exposure may be enrolled.

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 chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Any positive TB screen after the patient 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 test:

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD 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 are positive, the TB test is considered positive.

- The PPD Skin Test (also known as a TB Skin Test or Mantoux 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).
- 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 NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD are required per local guidelines) the PPD will be performed. 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 have an ulcerating reaction to the PPD in the past should not be re-exposed and the PPD should be considered positive.
- 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 patient 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 who reside 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 chest x-ray 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 chest x-ray not suggestive of active TB need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie Therapeutic Area Medical Director 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 a latent TB, 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 needs to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Of Note: Rifampicin or Rifapentine is 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 within 1 year prior to first study drug administration will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

Subjects with a documented completion of a full course of anti-TB therapy greater than 1 year prior to first study drug administration may be allowed to enter the study only after consultation with the AbbVie Therapeutic Area Medical Director.

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. TB prophylaxis should be initiated and study drug(s) should not be withheld. Two to four 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.

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

Annually for subjects with TB risk factors as identified by the TB risk assessment form (Appendix F) for subjects living in areas endemic for TB or for subjects with newly positive PPD and/or QuantiFERON-TB Gold test

Has been changed to read:

Annually (every 48 weeks) for subjects with newly identified TB risk factors based on the TB risk assessment form (Appendix F), or for subjects living in areas endemic for TB, or for subjects with newly positive PPD and/or QuantiFERON-TB Gold test.

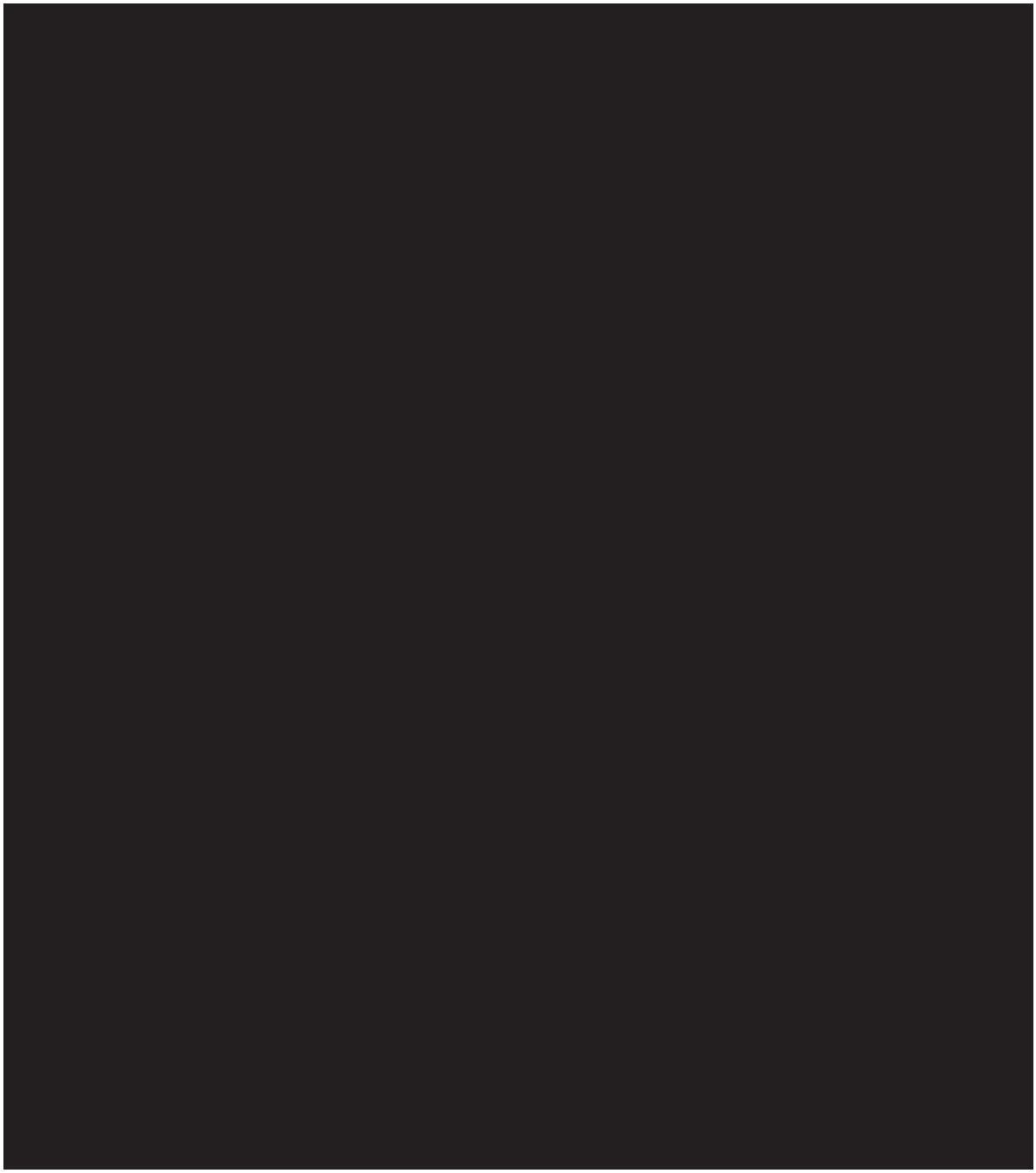
Section 5.3.1.1 Study Procedures
Subsection Chest X-Ray (CXR)
Last paragraph, first sentence previously read:

A radiologist must perform an assessment of the CXR.

Has been changed to read:

A radiologist or pulmonologist must perform an assessment of the CXR.

Section 5.3.1.1 Study Procedures
Subsection X-Rays of Hands and Feet
Bullet list previously read:



Has been changed to read:

Section 5.3.1.1 Study Procedures
Subsection X-Rays of Hands and Feet
Thirteenth paragraph previously read:

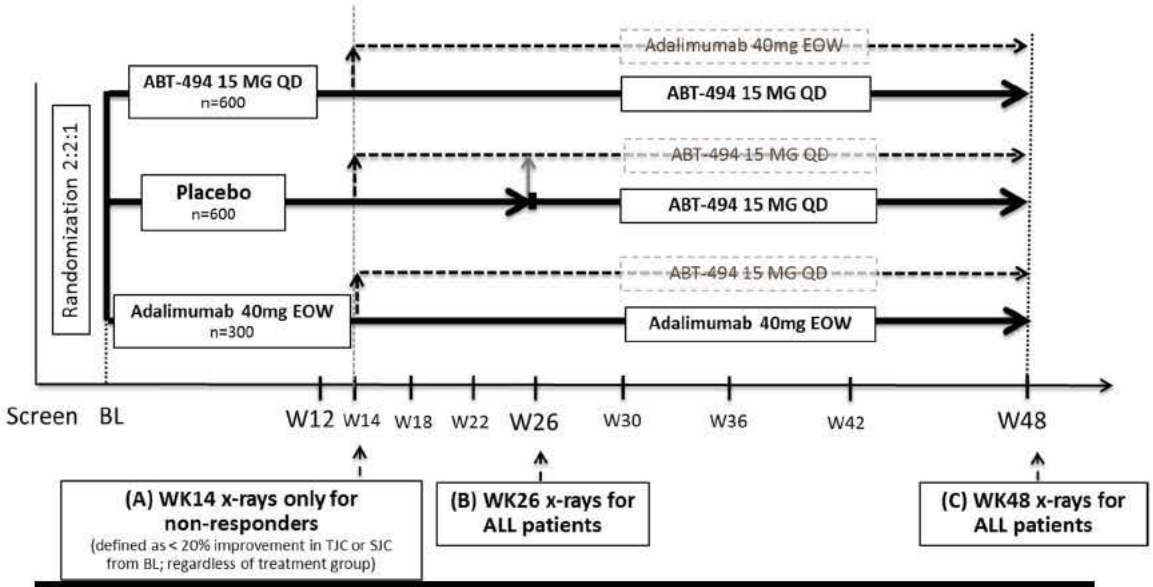
Overall in Period 1, each subject will undergo a maximum of 4 scheduled visits for x-ray examination of bilateral hands and feet (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 14 (only for non-responders at Week 14), Week 26, and Week 48/PD.

Has been changed to read:

Overall in Period 1, each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 14 (only for non-responders at Week 14), Week 26, and Week 48/PD; in addition, subjects who

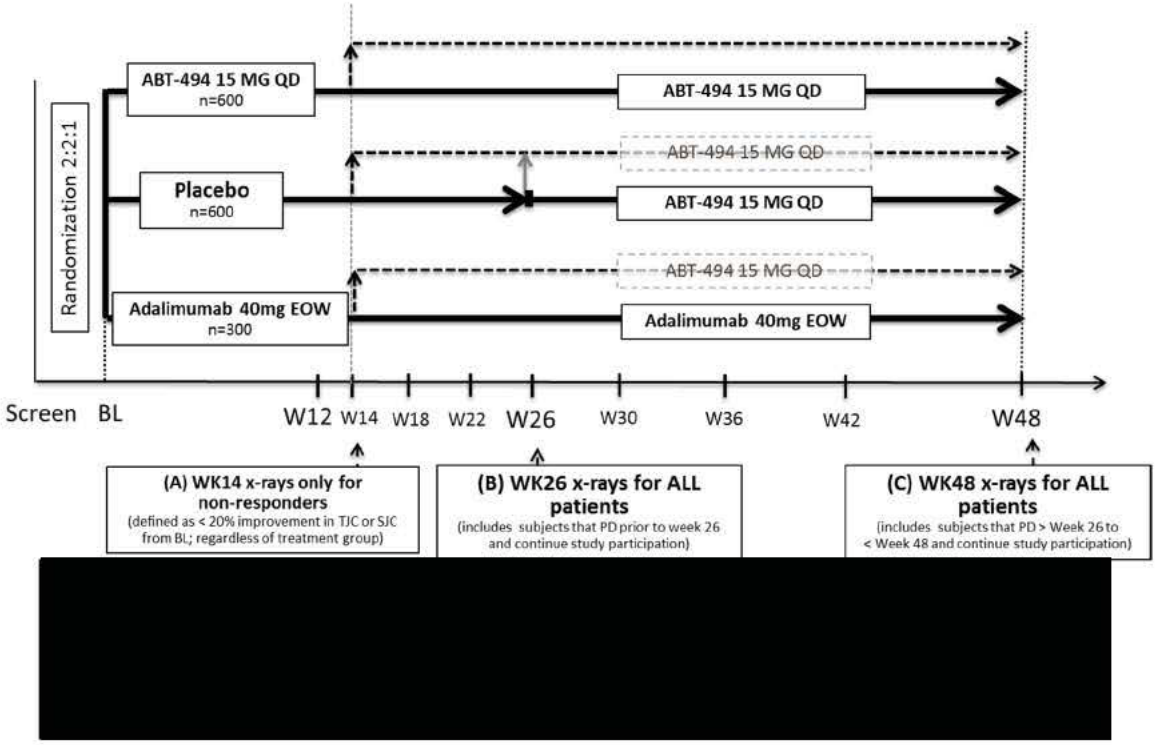
prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint.

Figure 3. Handling of X-Rays of Hands and Feet after Baseline (Period 1)
Previously read:



[redacted]

Has been changed to read:



Section 5.3.1.1 Study Procedures
Subsection Pregnancy Testing
Second paragraph, last bullet
Add: new last sentence

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.

Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests
Last paragraph
Add: new last sentence

Other laboratory abnormalities, including those which meet the toxicity management criteria outlined in Section 6.1.7 *(Toxicity Management)*, may be recorded as AEs at the discretion of the investigator.

Table 5. Clinical Laboratory Tests
Table note "i." and "k." previously read:

i. At screening for female subjects < 55 years old.

k. A urine pregnancy test will be performed for all female subjects 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. If a urine pregnancy test postbaseline 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.

Has been changed to read:

i. At screening for female subjects < 55 years old with no menses for ≥ 12 months AND no history of permanent surgical sterilization.

k. 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 minimum at monthly intervals (either at study visits or at home between scheduled study visits) (for details see Section 5.3.3.1.1 (Study Procedures).

Section 5.3.1.1 Study Procedures
Subsection <u>Hepatitis Screen</u>
Third paragraph, first and second bullet previously read:

- HBs Ag
- HBc Ab/anti-HBc

Has been changed to read:

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

Section 5.3.3.1.2 Key Secondary Variables
First paragraph previously read:

Key secondary endpoints (ABT-494 versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

Has been changed to read:

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

Section 5.3.3.1.2 Key Secondary Variables
Add: new second paragraph

Other key secondary endpoints (upadacitinib versus placebo) for US/FDA regulatory purposes are:

- ACR50 response rate at Week 12
- ACR70 response rate at Week 12
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26

Section 5.3.3.1.2 Key Secondary Variables
Second paragraph previously read:

Key secondary endpoints (ABT-494 versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

- Change from baseline in modified Total Sharp Score (mTSS) at Week 26;
- Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12;
- Change from baseline in DAS28 (CRP) at Week 12;
- Change from baseline in HAQ-DI at Week 12;
- ACR20 response rate at Week 12;
- ACR50 response rate at Week 12;
- ACR70 response rate at Week 12;
- Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of ABT-494 versus ADA);

- Change from baseline in SF-36 PCS at Week 12;
- Change from baseline in FACIT-F at Week 12;
- Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26;
- Change from baseline in RA-WIS at Week 12;
- Change from baseline in morning stiffness at Week 12.

Has been changed to read:

Ranked key secondary endpoints (upadacitinib versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

1. Change from baseline in modified Total Sharp Score (mTSS) at Week 26;
2. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12;
3. Change from baseline in DAS28 (CRP) at Week 12;
4. Change from baseline in HAQ-DI at Week 12;
5. ACR20 response rate at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of upadacitinib versus ADA);
7. Change from baseline in SF-36 PCS at Week 12;
8. Proportion of subjects achieving LDA based on Clinical Disease Activity Index (CDAI) at Week 12
9. Change from baseline in morning stiffness at Week 12;
10. Change from baseline in FACIT-F at Week 12.
11. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26;

Other key secondary endpoints (upadacitinib versus placebo) for EU/EMA regulatory purposes are:

- ACR50 response rate at Week 12
- ACR70 response rate at Week 12

Section 5.3.3.1.3 Additional Variables
First paragraph previously read:

Additional endpoints at all visits are:

Has been changed to read:

Additional endpoints (upadacitinib versus placebo and adalimumab) at all visits are:

Section 5.3.3.1.3 Additional Variables
Seventh bullet previously read:

Proportion of subjects achieving MCID in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3);

Has been changed to read:

- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.22;
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3;

Section 5.3.3.2 Period 2 Variables
First paragraph
Add: new fifth bullet

Change from baseline in CDAI and SDAI;

Section 5.3.3.2 Period 2 Variables
Add: new seventh and eighth bullet

- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.22;
- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3;

Section 5.4.1 Discontinuation of Individual Subjects
Last bullet previously read:

Starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

Has been changed to read:

Starting at Week 48, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) must be discontinued from study drug.

Section 5.4.1 Discontinuation of Individual Subjects
Add: new third paragraph

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment or study participation should complete a Premature Discontinuation visit (PD visit) as described in Section 5.1 (Overall Study Design and Plan: Description)

Section 5.4.1 Discontinuation of Individual Subjects
Delete: third and fourth paragraph

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should complete a Premature Discontinuation Visit (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 Table 2 and Table 4 and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood sample collection for optional exploratory research and validation studies. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply; this includes 20% TJC/SJC calculations at Weeks 14 – 22, and Week 48 and thereafter, as well as CDAI calculation at Week 26, if applicable. 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 Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. For subjects on subcutaneous study drug, if the subject is willing, a 70-day phone call may 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.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Fourth paragraph, last bullet, first sentence previously read:

If the subject experiences a study drug interruption > 14 consecutive days during Period 1 or > 30 consecutive days during Period 2 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from study drugs.

Has been changed to read:

If the subject experiences a study drug interruption > 14 consecutive days during the first 26 weeks, > 21 days between Week 26 and Week 48 or > 30 consecutive days during Period 2 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from study drugs.

Section 5.5.4 Selection and Timing of Dose for Each Subject
Fifth paragraph, last bullet, first sentence previously read:

If the subject experiences a study drug interruption of > 3 consecutive missed doses in Period 1 or 2 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from the study.

Has been changed to read:

If the subject experiences a study drug interruption of > 2 consecutive missed doses during the first 26 weeks or > 3 consecutive missed doses after Week 26 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from the study.

Section 5.5.5.1 Blinding of Investigational Product
First paragraph previously read:

All AbbVie personnel with direct oversight conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout Period 1.

Has been changed to read:

All AbbVie personnel with direct oversight, conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), will remain blinded to each subject's treatment through Week 26. The Investigator, study site personnel, and the subject will remain blinded to each subject's treatment in Period 1 until the last subject completes the last visit of Period 1 (Week 48).

Section 6.1.1.3 Adverse Events of Special Interest
Bullet list previously read:

- Serious infections, opportunistic infections, herpes zoster, and TB;
- Malignancy and lymphoproliferative disorders;
- Gastrointestinal perforations;
- Cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Lipid profile changes;
- Anemia and hemoglobin effects;
- Decreased neutrophil counts;
- Decreased lymphocyte counts;

- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Increased creatine phosphokinase (CPK).

Has been changed to read:

- Serious infections
- Opportunistic infections
- Herpes Zoster
- Tuberculosis
- Malignancy (all types)
- Gastrointestinal Perforations
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
- Lipid Profile Changes
- Anemia
- Neutropenia
- Lymphopenia
- Increased serum creatinine and renal dysfunction
- Hepatic events and increased hepatic transaminases
- Elevated creatine phosphokinase (CPK)
- Embolic and thrombotic events (non-cardiac, non-CNS)

Section 6.1.3 Relationship to Study Drug
"Reasonable Possibility" and "No Reasonable Possibility" previously read:

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

Has been changed to read:

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.

Section 6.1.3 Relationship to Study Drug
Second paragraph, previously read:

For relationship 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 relationship or deemed it not assessable, AbbVie will consider the event associated.

Has been changed to read:

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.

Section 6.1.4 Adverse Event Collection Period
Fourth paragraph
Delete: last bullet

Cardiovascular procedures (SAE Supplemental Procedure eCRF).

Section 6.1.4 Adverse Event Collection Period
Fifth paragraph
Add: new last bullet

Embolic and thrombotic events (non-cardiac, non-CNS).

Section 6.1.5 Serious Adverse Event Reporting
Last paragraph, first sentence previously read:

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

Has been changed to read:

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.

Section 6.1.7 Toxicity Management
Third paragraph, sixth and seventh 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. Subjects who develop active TB 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 the first 26 weeks, more than 21 days between Weeks 26 and 48 or more than 30 consecutive days thereafter, the subject must be discontinued from study drug. Subjects who develop active TB must be permanently discontinued from study drug.

Section 6.1.7 Toxicity Management
Fourth paragraph, first sentence previously read:

Serious Gastrointestinal Events: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation.

Has been changed to read:

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation.

Section 6.1.7 Toxicity Management
Fifth paragraph, first sentence previously read:

Cardiovascular Events (MACE): Subjects presenting with potential cardiovascular events should be carefully monitored.

Has been changed to read:

Cardiovascular Events: Subjects presenting with potential cardiovascular events should be carefully monitored.

Section 6.1.7 Toxicity Management
Seventh paragraph previously read:

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant OR a confirmed absolute QTcF value > 500 msec.

Has been changed to read:

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.

Section 6.1.7 Toxicity Management
Eighth paragraph
Add: new third and fourth sentence

All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 7, the repeat testing must occur as soon as possible.

Table 7. Specific Toxicity Management Guidelines for Abnormal Laboratory Values "AST or ALT," "Serum Creatinine," and "Creatine Phosphokinase" previously read:

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Discontinue study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5. • INR will only be measured in subjects with ALT or AST > 3 × 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 × 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 × ULN by repeat testing with new sample. • Discontinue study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. For all of the above ALT or AST elevation scenarios, complete supplemental hepatic eCRF.
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value, 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 ≤ 1.5 × baseline value. • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. • For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
Creatine Phosphokinase	• If any confirmed CPK value ≥ 4 × ULN (if symptomatic or asymptomatic), complete supplemental CPK eCRF. • If confirmed CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug, complete supplemental CPK eCRF, and contact AbbVie TA MD.

Has been changed to read:

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5. o A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug immediately if confirmed ALT or AST > 3 × 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%). • Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • Interrupt study drug immediately if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF. • Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within 1 week: o ALT > 5 × ULN OR o ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR o ALT or AST > 3 × ULN along with clinical signs of possible hepatitis A positive result for HBV DNA PCR testing in these subjects will require immediate interruption of study drug and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and > 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 ≤ 1.5 × baseline value and ≤ ULN. • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
Creatine Phosphokinase	• If confirmed CPK ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD For the above CPK elevation scenarios, complete supplemental CPK eCRF.

Section 6.2.2 Reporting
First paragraph, first sentence previously read:

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form.

Has been changed to read:

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.

Section 7.0 Protocol Deviations
"Primary Contact:" and "Alternate Contact:' previously read:

Primary Contact: Alternate Contact:

Has been changed to read:

Primary Contact:	Alternate Contact:
[redacted]	

Section 8.1 Statistical and Analytical Plans
Second paragraph, last sentence previously read:

Another unblinded analysis may be conducted for regulatory purposes after all subjects have completed Period 1 (Week 48).

Has been changed to read:

Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

Section 8.1.2.3 Study Drug Exposure
Last paragraph previously read:

Study drug compliance will be summarized for each treatment group for Period 1. 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 in Period 1 divided by the number of tablets a subject is supposed to take each day times the length of time that the subject was in the Treatment Phase of Period 1.

Has been changed to read:

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 in Period 1 divided by the number of tablets a subject is supposed to take each day times the length of time that the subject was in the Treatment Phase.

Section 8.1.4.1.2 Key Secondary Efficacy Variables
Fourth paragraph, last sentence previously read:

For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of ABT-494 vs adalimumab will also be tested for US/FDA purposes.

Has been changed to read:

For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of upadacitinib vs adalimumab will also be tested.

Section 8.1.4.1.4 Multiplicity Control for the Primary and Key Secondary Endpoints
Section title and text previously read:

8.1.4.1.4 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.

Has been changed to read:

8.1.4.1.4 Multiplicity Control for the Primary and Ranked Key Secondary Endpoints

In order to preserve Type I error, a step-down approach will be used to test the primary and ranked 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.

Section 8.1.4.1.5 Imputation Methods
Fourth paragraph, last sentence previously read:

In NRI analysis, subjects who prematurely discontinue study drug will be considered non-responders on or after discontinuation date.

Has been changed to read:

In NRI analysis, subjects who prematurely discontinue study drug will be considered non-responders after discontinuation.

Section 8.1.4.1.5 Imputation Methods
Fifth paragraph previously read:

Linear Extrapolation for Radiographic Data: For radiographic data (i.e., mTSS-based endpoints), if a subject escapes at Week 14 or prematurely discontinued before Week 26, their Week 26/48 data will be imputed assuming a linear relationship between baseline and previous time point when x-ray should be collected.

Has been changed to read:

Linear Extrapolation for Radiographic Data: For radiographic data (i.e., mTSS-based endpoints), if a subject is rescued at Week 14 to a different study drug or prematurely discontinued study drug, their Week 26/48 data will be imputed assuming a linear relationship between baseline and previous x-ray collected at the time of rescue/PD.

Section 8.1.5.1 General Considerations
First paragraph, last sentence previously read:

Analyses will be conducted for Period 1 alone, as well as for Period 1 and Period 2 combined.

Has been changed to read:

Analyses will be conducted for both short term and long term.

Section 8.1.5.2 Analysis of Adverse Events
Previously read:

Unless otherwise specified, the following conventions apply for both the Period 1 safety analysis and the combined safety analysis of Period 1 and Period 2.

Has been changed to read:

Unless otherwise specified, the following conventions apply for both short term and long term safety analysis.

Section 8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)
Second paragraph, last sentence previously read:

For subjects who continued into Period 2, the AEs that are reported in Period 2 will be summarized in the combined safety analysis of Period 1 and Period 2.

Has been changed to read:

For subjects who continued into Period 2, the AEs that are reported in Period 2 will be summarized in the long term safety analysis.

Section 8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)
Fifth and sixth bullet previously read:

- 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);

Has been changed to read:

- Frequent AEs (reported in 2% of subjects or more in any treatment group);
- Frequent reasonably possibly related AEs (reported in 2% of subjects or more in any treatment group);

Section 8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)
Seventh paragraph, first sentence previously read:

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.

Has been changed to read:

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

Section 8.1.5.3 Analysis of Laboratory, Vital Sign, and ECG Data
First paragraph, first sentence previously read:

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

Has been changed to read:

Changes from baseline by visit in continuous laboratory data, and vital signs will be summarized by treatment group.

Section 8.1.5.3 Analysis of Laboratory, Vital Sign, and ECG Data
Second paragraph, second sentence previously read:

For creatinine phosphokinase, serum creatinine, and parameters that are not covered in the OMERACT criteria, NCI CTC criteria will be used.

Has been changed to read:

For creatine phosphokinase, and serum creatinine, NCI CTC criteria will be used.

Section 8.2 Determination of Sample Size
Last sentence previously read:

It will also provide at least 90% power in testing superiority of ABT-494 versus placebo for most of the ranked secondary endpoints, including change from baseline in DAS28 (CRP), change from baseline in HAQ-DI, ACR50 and ACR70 response rate, and SF-36 (PCS), at two sided significance level of 0.05 and accounting for a 10% dropout rate.

Has been changed to read:

It will also provide at least 90% power in testing superiority of upadacitinib versus placebo for most of the key secondary endpoints, including change from baseline in DAS28 (CRP), change from baseline in HAQ-DI, ACR50 and ACR70 response rate, and SF-36 (PCS), at two-sided significance level of 0.05 and accounting for a 10% dropout rate.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacokinetics and Pharmacodynamics
		Clinical Program Development
		Global Clinical Drug Supply
		Clinical Program Development

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacokinetics and Pharmacodynamics
		Bioanalysis
		Clinical Program Development
		Clinical Program Development

Appendix C. Local Requirements
Criterion 12 and 13 previously read:

12. If female of childbearing potential, must be practicing at least two reliable methods of contraception (one highly effective method combined with one effective method, refer to Section 5.2.4), that are effective from Study Day 1 through at least

150 days after the last dose of subcutaneous study drug and through at least 30 days after the last dose of oral study drug.

13. If male, and subject is sexually active with the 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).

Has been changed to read:

12. If female of childbearing potential, must be practicing at least two reliable methods of contraception (one highly effective method combined with one effective method, refer to Section 5.2.4), that are effective from Study Day 1 through at least 150 days after the last dose of subcutaneous study drug, through at least 30 days after the last dose of oral study drug, and through 180 days after the last dose of methotrexate. If more than one of the above intervals apply, the longest interval must be adhered to.

13. If male, and subject is sexually active with the female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of oral study drug and through 90 days after the last dose of methotrexate, to practice the protocol-specified contraception (refer to Section 5.2.4). The same intervals apply to abstention from sperm donation. If more than one of the above intervals apply, the longest interval must be adhered to.

Appendix C. Local Requirements
Subsection <u>Contraception Recommendation for Females</u>
Third paragraph, last sentence previously read:

That is effective from Study Day 1 (or earlier) through at least 150 days after the last dose of subcutaneous study drug and through at least 30 days after the last dose of oral study drug.

Has been changed to read:

That is effective from Study Day 1 (or earlier) through at least 150 days after the last dose of subcutaneous study drug, through at least 30 days after the last dose of oral study drug, and through 180 days after the last dose of methotrexate. If more than one of the above intervals apply, the longest interval must be adhered to:

Appendix C. Local Requirements
Subsection Contraception Recommendation for Males
Second paragraph previously read:

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 oral study drug to practice contraception with:

Has been changed to read:

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 oral study drug and through 90 days after the last dose of methotrexate to practice contraception with:

Appendix C. Local Requirements
Subsection Contraception Recommendation for Males
Third paragraph previously read:

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

Has been changed to read:

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 30 days after the last dose of oral study drug and through 90 days after the last dose of methotrexate.

Appendix F. Latent TB Risk Assessment Form Example
Criterion 2, 3, and 4 previously read:

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

Has been changed to read:

2. Have you lived in or had prolonged travels to countries in the following regions:
    - Sub-Saharan Africa
    - India
    - China
    - Mexico

- Southeast Asia or Micronesia
- The former Soviet Union

3. Have you lived or worked in a prison, homeless shelter, immigration center, 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
    - Production of Sputum
    - Blood-Streaked Sputum
    - Unexplained Weight Loss
    - Fever
    - Fatigue/Tiredness
    - Night Sweats
    - Shortness of Breath

Appendix O. Rheumatology Common Toxicity Criteria v.2.0 Example "2 – Moderate" previously read:

2 – Moderate
No medication or OTC
Symptomatic
Duration (1 – 2 weeks)
Alter lifestyle occasionally
Meds relieve. (may be prescription),
Study drug continued

Has been changed to read:

2 – Moderate
Symptomatic
Duration (1 – 2 weeks)
Alter lifestyle occasionally
Meds relieve. (may be prescription),
Study drug continued

Appendix O. Rheumatology Common Toxicity Criteria v.2.0 Example
Subsection L. Chemistry
"L9." and "L11." previously read:

L. Chemistry				
L9. CPK (also if polymyositis-disease	1.2 – 1.9 × ULN	2.0 – 4.0 × ULN	4.0 × ULN with weakness but without life-threatening signs or symptoms	> 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening
L11. Creatinine (mg/dl)	1.1 – 1.3 × ULN	1.3 – 1.8 × ULN	1.9 – 3.0 × ULN	> 3.0 × ULN

Has been changed to read:

L. Chemistry				
L9. CPK (also if polymyositis-disease)*	1.2 – 1.9 × ULN	2.0 – 4.0 × ULN	4.0 × ULN with weakness but without life-threatening signs or symptoms	> 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening
L11. Creatinine (mg/dl)*	1.1 – 1.3 × ULN	1.3 – 1.8 × ULN	1.9 – 3.0 × ULN	> 3.0 × ULN

Appendix O. Rheumatology Common Toxicity Criteria v.2.0 Example
Add: new table note "*."

* For CPK and Creatinine NCI CTC grading will be used. For CPK the following gradings apply: Grade 1: > ULN – 2.5 × ULN; Grade 2: > 2.5 – 5.0 × ULN; Grade 3: > 5.0 – 10.0 × ULN; Grade 4: > 10.0 × ULN; For Creatinine the following gradings apply: Grade 1: > 1 – 1.5 × Baseline; > ULN – 1.5 × ULN; Grade 2: > 1.5 – 3.0 × Baseline; > 1.5 – 3.0 × ULN; Grade 3: > 3.0 baseline; > 3.0 – 6.0 × ULN; Grade 4: > 6.0 × ULN

Document Approval

Study M14465 - A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR) - Amendment 5 - EudraCT 2015-003333-95 - 01Dec2017

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