1.0 Title Page

Clinical Study Protocol M13-549

A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs

Incorporating Amendments 0.01 (Canada Only), 1, 1.01 (Korea Only), 1.01.01 (Korea Only), 2, 2.01 (Korea Only), 2.02 (Canada Only), 3, 4, 5, 6, 6.01 (VHP Countries, LT and GR), 7 and 8

AbbVie Investigational Product:	Upadacitinib
Date:	25 November 2020
Development Phase:	3
Study Design:	A 12-week randomized, double-blind, parallel-group, placebo-controlled period followed by a blinded long-term extension period
EudraCT Number:	2015-003332-13
Investigators:	Multicenter trial (Investigator information is on file at AbbVie)
Sponsor:	AbbVie* 1 North Waukegan Road North Chicago, IL 60064

Sponsor/Emergency Medical Contact:	[redacted] MD Therapeutic Area Medical Director AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Office: Mobile: [redacted] Fax: Email: [redacted] Emergency 24 hour Number: +1 973-784-6402

* 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
Amendment 0.01 (Canada Only)	06 January 2016
Amendment 1.01 (Korea Only)	15 March 2016
Amendment 1.01.01 (Korea Only)	07 April 2016
Amendment 1.02 (France Only)	20 April 2016
Amendment 2	01 April 2016
Amendment 2.01 (Korea Only)	23 May 2016
Amendment 2.02 (Canada Only)	01 June 2016
Amendment 3	31 March 2017
Amendment 3.01 (France Only)	14 April 2017
Amendment 4	21 June 2017
Amendment 4.01 (France Only)	31 July 2017
Amendment 5.01 (France Only)	14 December 2017
Amendment 5.01.01 (France Only)	07 December 2018
Amendment 6	16 December 2019
Amendment 6.01 (VHP Countries, LT and GR)	06 March 2020
Amendment 7	15 July 2020

The purpose of this amendment is to:

- Apply administrative changes throughout the protocol.

  Rationale: *Revised text to improve consistency and readability, and/or provide clarification.*
- Update Section 1.2, Synopsis

  Rationale: *Revised to be consistent with Amendment 8 revisions.*
- Update Section 1.3, List of Abbreviations

Rationale: *Updated to include new terms, Direct-to Patient (DTP) and Coronavirus Disease – 19 (COVID-19)*

- Update Section 3.2, Benefits and Risks

  Rationale: *Revised to include the evaluation of the benefit and risk to subjects participating in the study relative to COVID-19.*

- Update Section 5.1, Overall Study Design and Plan: Description

  Rationale: *Added provisions for virtual or alternative locations for study visits in the event of a pandemic situation like COVID-19 or any state of emergency (e.g., natural disaster, conflict/combat) to ensure the safety of subjects and site staff, while maintaining the integrity of the study.*

- Update Section 5.2.3.2, Prohibited Therapy

  Rationale: *Revised Table 1 to update the list of examples of commonly used strong cytochrome 3A inducers.*

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

  Rationale: *Added clarifications on study activities that can be performed by phone/video conference or at local clinic/hospital/laboratory or through the optional home healthcare service in the event study visits are impacted by any state of emergency or pandemic situation like COVID-19 to ensure subjects' safety and study continuation, as permitted by IRB/IEC.*

- Update Section 5.3.1.1, Study Procedures
  - Outcomes and Questionnaires

    Specified that questionnaires are not eligible for completion by virtual interview in the event that an onsite visit cannot be performed due to a pandemic or state of emergency and will be completed at the next earliest feasible visit.

  - TB (tuberculosis) Testing/TB Prophylaxis and Chest X-rays (CXR)

    Specified that chest X-rays can be performed at the next earliest feasible visit unless the Investigator has determined that a CXR is required to ensure that it is safe to continue study drug administration (e.g., subjects with seroconversion on an annual TB test). In this case, the Investigator should contact the AbbVie Therapeutic Area Medical Director (TA MD) to

determine if the subject may continue on study drug and CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

- 12-Lead Electrocardiogram (ECG)

  Specified that the 12-Lead ECG can be performed at the next earliest feasible visit unless the Investigator has determined that an ECG is required to ensure that it is safe to continue study drug administration. In this case, the ECG should be performed as soon as restrictions allow at the study site or local hospital/facility.

- Physical Exam

  Added provision allowing the complete physical exam to be performed at the next earliest feasible visit.

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

  Specified that Physician Global Assessment of Disease Activity is not eligible for completion by virtual interview in the event that the subject cannot perform an onsite visit due to a pandemic or state of emergency and will be completed by the physician at the next earliest feasible subject's visit.

- Tender Joint Count (TJC) and Swollen Joint Count (SJC) Assessments

  Added provision allowing the TJC and SJC to be performed at the next earliest feasible visit by the independent joint assessor, if possible.

- Pregnancy Test

  Added provision allowing the urine pregnancy test to be performed at a local laboratory or at home. Removed the reference to contraception requirements for male subjects with a partner of childbearing potential for consistency with Section 5.2.4 "Contraception Recommendations."

- Clinical Laboratory Tests

  Added provision allowing the laboratory testing at an alternate local facility, in the event that a state of emergency or pandemic prevents the subject from performing the central laboratory tests and added the

requirements to allow the study drug dispensation when laboratory tests are performed at a local laboratory.

- Study Drug Dispensing, Dosing and Compliance

  Added provision allowing Direct-to-Patient (DTP) shipment of study drug and study ancillaries due to state of emergency or pandemic situations.

- New Section: Optional Home Healthcare Service Due to State of Emergency or Pandemic Situation like COVID-19

  Added home healthcare visits as an option in case a study visit on site cannot be performed due to state of emergency or pandemic-related reasons.

Rationale: *To modify study visits and protocol-specific procedures impacted by the COVID-19 or any pandemic/state of emergency as necessary, to ensure the safety of subjects/site staff and study continuation including alternative locations for data collection, as permitted by IRB/IEC.*

- Update Section 5.4.1, Discontinuation of Individual Subjects

  Rationale: *Revised to clarify that subjects will have to discontinue study drug treatment immediately if they develop a gastrointestinal perforation with the exception of appendicitis or mechanical injury to be consistent with the Section 6.1.7 "Toxicity Management."*

  Clarified that the state of emergency and pandemic-related restrictions may allow mitigation strategies to ensure subject safety and continuity of care as an alternative to study discontinuation/study drug discontinuation and that the AbbVie TA MD should be contacted before discontinuing a subject to ensure all acceptable mitigation steps have been explored.

- Update Section 5.5.1, Treatments Administered

  Rationale: *Added specifications in order to provide the study drug through DTP shipment in the event pandemic situation like COVID-19 or state of emergency prevent the study drug dispensation to the subject onsite, if permitted by local regulations.*

- Update Section 6.1.1.3, Adverse Events of Special Interest

  Rationale: *Clarified and updated the list of the adverse events of special interest according to the revised sponsor guidelines.*

- Update Section 6.1.4, Adverse Event Collection Period

  Rationale: *Added supplemental COVID-19 case report forms for missed or virtual visits, study drug interruptions or discontinuations, or adverse events and instructions to collect safety information related to COVID-19.*

- Update Section 6.1.5, Serious Adverse Event Reporting

  Rationale: *Updated telephone number to contact the Immunology Safety Team for safety concerns.*

- Update Section 6.1.6, Pregnancy

  Rationale: *Updated text to define Pregnancy reporting timeline as 24 hours from site staff awareness according to the sponsor requirements.*

- Update Section 6.1.7, Toxicity Management

  Rationale: *Added guidance for investigators on the management of subjects with suspected or confirmed COVID-19 infection during the study. Clarified that the Investigator should also contact the AbbVie TA MD for confirmed ALT or AST > 8 x ULN in addition to the immediate study drug interruption.*

- Update Section 6.2.2, Reporting

  Rationale: *Updated text to define Product Complaint reporting timeline as 24 hours from site staff awareness according to the sponsor requirements.*

- Update Section 7.0, Protocol Deviations

  Rationale: *Added language to include provision for modifications due to protocol deviations that may be due to pandemic like COVID-19 or state of emergency situations in order to guide investigators to notify IRB/EC when deviations occur.*

- Update Section 9.2, Ethical Conduct of the Study

  Rationale: *Inclusion of information regarding COVID-19 or any pandemic/state of emergency-related acceptable protocol modifications.*

- Update Section 9.3, Subject Information and Consent

  Rationale: *Added provision that in the event of a pandemic situation or state of emergency, verbal consent may be obtained in addition to the study informed consent in accordance with local regulations.*

- Update Section 10.1, Source Documents

Rationale: *Noted that remote monitoring may be employed as needed, due to COVID-19 or any pandemic/state of emergency.*

- Update Appendix A, Responsibilities of the Clinical Investigator

  Rationale: *Clarified that clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP).*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Update list of current Protocol Signatories.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-549
Name of Study Drug: Upadacitinib	**Phase of Development:** 3
Name of Active Ingredient: Upadacitinib	**Date of Protocol Synopsis:** 25 November 2020
Protocol Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs	
Objectives: **Period 1** 1. To compare the efficacy of upadacitinib 30 mg once daily (QD) and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active rheumatoid arthritis (RA) who are on a stable dose of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and have an inadequate response to csDMARDs. 2. To compare the safety and tolerability of upadacitinib 30 mg QD and 15 mg QD versus placebo in subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. **Period 2** To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1.	
Investigators: Multicenter	
Study Sites: Approximately 230	
Study Population: 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/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) ≥ 3 mg/L (central lab) at Screening. Subjects must have been on a stable dose of csDMARD therapy (restricted to methotrexate [MTX], chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug. Subjects with inadequate response to hydroxychloroquine and/or chloroquine can only be included if they also failed MTX, sulfasalazine, or leflunomide.	
Number of Subjects to be Enrolled: Approximately 600	

Methodology:

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1. Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

The study duration will include a 35-day screening period; a 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a 248 week blinded long-term extension period (Period 2); and a 30-day follow-up period.

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

- Group 1: Upadacitinib 30 mg QD (N = 200) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 2: Upadacitinib 15 mg QD (N = 200) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: Placebo (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Subjects must have been on a stable dose of csDMARD(s) for ≥ 4 weeks prior to the first dose of study drug and must remain on a stable dose until Week 24; the csDMARD dose may be decreased only for safety reasons. Starting at Week 24 (after Week 24 assessments have been performed), initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or adding or increasing doses of 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) 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 limited exposure (< 3 months), OR response to 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, as determined by the Investigator, are not eligible.

Subjects who complete the Week 12 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2 (248 weeks). Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments. Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

At Week 24, if a subject fails to meet Low Disease Activity (LDA) criterion (LDA defined as CDAI ≤ 10) investigator should adjust the subject's background RA therapies.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study.

Methodology (Continued):

Study visits may be impacted by state of emergency or pandemic like COVID-19. If visits cannot be conducted onsite due to travel restrictions or other pandemic or state of emergency related reasons, virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others may be performed. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

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 also fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects have been receiving csDMARD therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug.
   - Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide.
   - Subjects with inadequate response to hydroxychloroquine and/or chloroquine can only be included if they have also failed MTX, sulfasalazine, or leflunomide.
   - The following csDMARDs are allowed (stable dose for ≥ 4 weeks prior to the first dose of study drug): oral or parenteral MTX (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 15 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day).
   - A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide
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 ≥ 3 mg/L (central lab) at Screening Visit.
5. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of study population). Specifically, prior to enrollment.
   a. Subjects with limited exposure to bDMARD (< 3 months) OR
   b. Subjects who are responding to bDMARD therapy but had to discontinue due to intolerability (regardless of treatment duration).

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 are considered inadequate responders to bDMARD therapy as determined by the Investigator.
3. History 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 × upper limit of normal (ULN); serum alanine transaminase > 2 × ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73 m^2; total white blood cell count < 2,500/µL; absolute neutrophil count < 1,500/µL; platelet count < 100,000/µL; absolute lymphocyte count < 850/µL; and hemoglobin < 10 g/dL.

Investigational Product:	Upadacitinib
Doses:	15 mg QD 30 mg QD
Mode of Administration:	Oral
Reference Therapy:	Matching placebo for upadacitinib QD
Dose:	N/A
Mode of Administration:	Oral

Duration of Treatment: 260 weeks (Period 1: 12 weeks; Period 2: 248 weeks)

Criteria for Evaluation:

Efficacy:

Period 1

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response (US/FDA regulatory purposes) or the proportion of subjects achieving low disease activity (LDA) (EU/EMA regulatory purposes) at Week 12.

ACR20 response rate will be determined based on 20% or greater improvement in Tender Joint Count (TJC) and Swollen Joint Count (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.

LDA is defined as Disease Activity Score (DAS)28 (C-reactive protein [CRP]) ≤ 3.2.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Period 1 (Continued)

Ranked key secondary endpoints (at Week 12) for US/FDA regulatory purposes are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. Change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS);
4. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2;
5. Proportion of subjects achieving Clinical remission (CR) based on DAS28 (CRP);
6. Proportion of subjects achieving LDA based on CDAI ≤ 10;
7. Change from baseline in morning stiffness
8. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F);

Ranked key secondary endpoints (at Week 12) for EU/EMA regulatory purposes are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. ACR20 response rate;
4. Change from baseline in SF-36 PCS;
5. Proportion of subjects achieving CR based on DAS28 (CRP);
6. Proportion of subjects achieving LDA based on CDAI ≤ 10;
7. Change from baseline in morning stiffness
8. Change from baseline in FACIT-F;

Other key secondary endpoints (at Week 12, if not specified) for both US/FDA and EU/EMA regulatory purposes are:

- ACR50 response rate;
- ACR70 response rate;
- ACR20 response rate at Week 1

Additional endpoints 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;
- Change from baseline in morning stiffness;
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria (see below);
- Proportion of subjects achieving minimum clinically important difference (MCID) in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3);
- ACR/EULAR Boolean remission;
- Change from baseline in EQ-5D-5L;
- Change from baseline in SF-36;

Criteria for Evaluation (Continued):

Efficacy (Continued):

Period 1 (Continued)

- Change from baseline in FACIT-F;
- Change from baseline in RA-WIS.

	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 16, 20, 24, 36, 48, every 12 weeks through Week 240, and Week 260/PD:

- 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 achieving MCID in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3);
- ACR/EULAR Boolean remission;
- Concomitant corticosteroid use (systemic use and intra-articular injections).

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 24 and 48 only:

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

Pharmacokinetic (Period 1 Only):

Blood samples for assay of upadacitinib and possibly other concomitant medications in plasma will be collected at Weeks 1, 2, 4, 8, and 12/Premature Discontinuation.

In Vivo Pharmacodynamic Biomarkers (Periods 1 and 2):

Period 1

Change from baseline in lymphocyte subsets (including but not limited to natural killer cells, natural killer T cells, B cells, and T cells) will be evaluated at Weeks 8 and 12/Premature Discontinuation.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Period 2

Change from baseline in lymphocyte subsets (including but not limited to natural killer cells, natural killer T cells, B cells, and T cells) will be evaluated at Weeks 16, 24, 36, 48, and every 24 weeks thereafter.

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:

Comparisons of the primary and key secondary efficacy endpoints will be made between each upadacitinib group and the combined placebo groups. The overall type I error rate of the primary and ranked key secondary endpoints for the two doses will be strongly controlled.

For binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparisons between each upadacitinib group and the combined placebo groups will be conducted using the Cochran-Mantel-Haenszel test adjusting for main stratification factors.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between each of the upadacitinib treatment groups and the combined placebo groups 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.

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 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.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ACR	American College of Rheumatology
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-CCP	anti-cyclic citrullinated peptide
AST	aspartate transaminase
BCG	Bacille Calmette-Guérin
bDMARD	biological disease-modifying anti-rheumatic drug
BID	twice daily (Latin: bis in die)
BUN	blood urea nitrogen
CBC	complete blood count
CD4, CD8	cluster of differentiation
CDAI	clinical disease activity index
CL/F	apparent clearance
COVID-19	Coronavirus Disease – 2019
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
CYP3A	cytochrome P450 3A
DAS	disease activity score
DMARD	disease-modifying anti-rheumatic drug
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DTP	Direct-to-Patient
ECG	electrocardiogram
eCRF	electronic case report form

EDC	electronic data capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
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
FSH	follicle stimulating hormone
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
ICF	informed consent form
ICH	International Conference On Harmonization
IEC	independent ethics committee
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
INR	international normalized ratio
IR	immediate release
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus activated kinase

LDA	low disease activity
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular event
MCID	minimum clinically important difference
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
MTX-IR	methotrexate inadequate responder
NA	no assessment
NK	natural killer
NKT	natural killer-T
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

RNA	Ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SDAI	Simple Disease Activity Index
SF-36	Short Form-36
SJC	swollen joint count
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
VTE	venous thromboembolic events
WBC	white blood cell

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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, 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 AEs (≥ 5%) in the upadacitinib treated subjects were urinary tract infection, headache, upper respiratory tract infection, and nausea. There were 6 subjects (1.3% of total combined populations) with herpes zoster reactivation distributed across the upadacitinib dose groups, and 2 subjects (1.9%) in the placebo groups. In these two 12 week studies, a total of 2 subjects in the upadacitinib treatment groups reported malignancies. One subject reported non-melanoma skin cancers (NMSC) (basal cell and squamous cell carcinoma) and 1 subject was diagnosed with lung cancer 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 M13-549 differs from other upadacitinib studies as it is the first study to evaluate the safety and efficacy of upadacitinib in the csDMARD inadequate responder population.

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.

In view of the COVID-19 pandemic, the benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

4.0 Study Objectives

Period 1

To compare the efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.

To compare the safety and tolerability of upadacitinib 30 mg QD and 15 mg QD versus placebo in subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.

Period 2

To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 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 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD and 15 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in subjects with RA who have completed Period 1. Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

The study is designed to enroll approximately 600 subjects at approximately 230 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 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a 248-week blinded long-term extension period (Period 2); and a 30-day follow-up period (call or visit).

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

- Group 1: Upadacitinib 30 mg QD (N = 200) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 2: Upadacitinib 15 mg QD (N = 200) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: Placebo (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)

- Group 4: Placebo (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Subjects must have been on a stable dose of csDMARD(s) for ≥ 4 weeks prior to the first dose of study drug and must remain on a stable dose until Week 24; the csDMARD dose may be decreased only for safety reasons.

At Week 24, if a subject fails to meet the Low Disease Activity (LDA) criterion (LDA defined as CDAI ≤ 10) the investigator should adjust the subject's background RA therapies. Starting at Week 24 (after Week 24 assessments have been performed) and thereafter, initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or adding or increasing doses of csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label. Starting at Week 24, at least 20% improvement in BOTH TJC AND SJC is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) (see Section 5.2.3.1) must be discontinued from study drug.

Subjects with prior exposure to at most one bDMARD for RA may be enrolled in the study (up to 20% of total study population) after the required washout period (for washout periods, see inclusion criterion 7, Section 5.2.1) is satisfied and if they have limited exposure (< 3 months), OR response to 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, as determined by the Investigator, are not eligible.

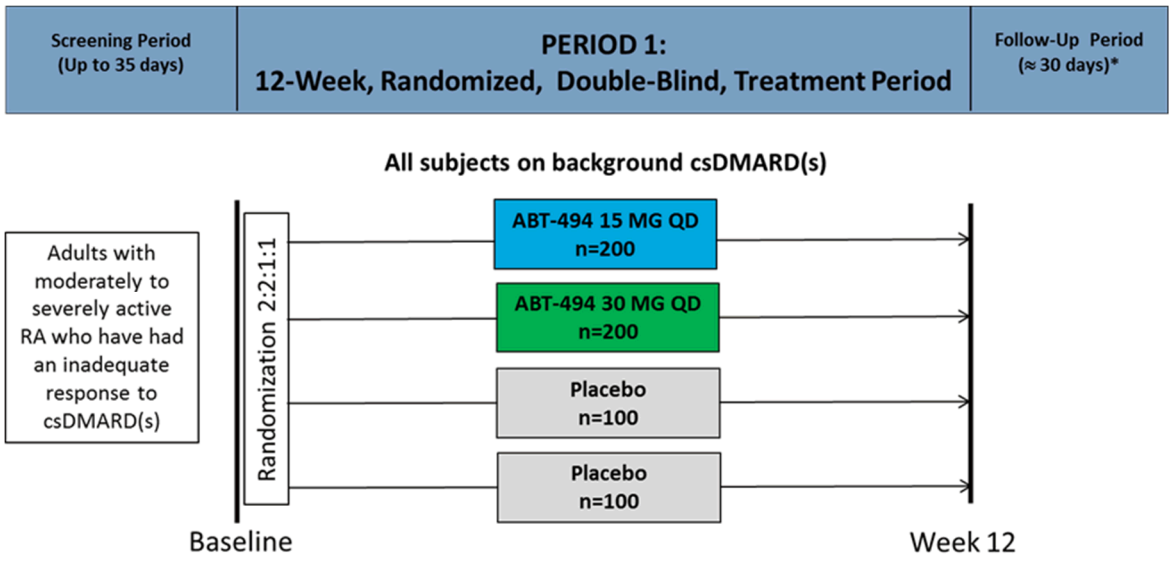
Subjects who complete the Week 12 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2 (248 weeks). Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study.

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

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

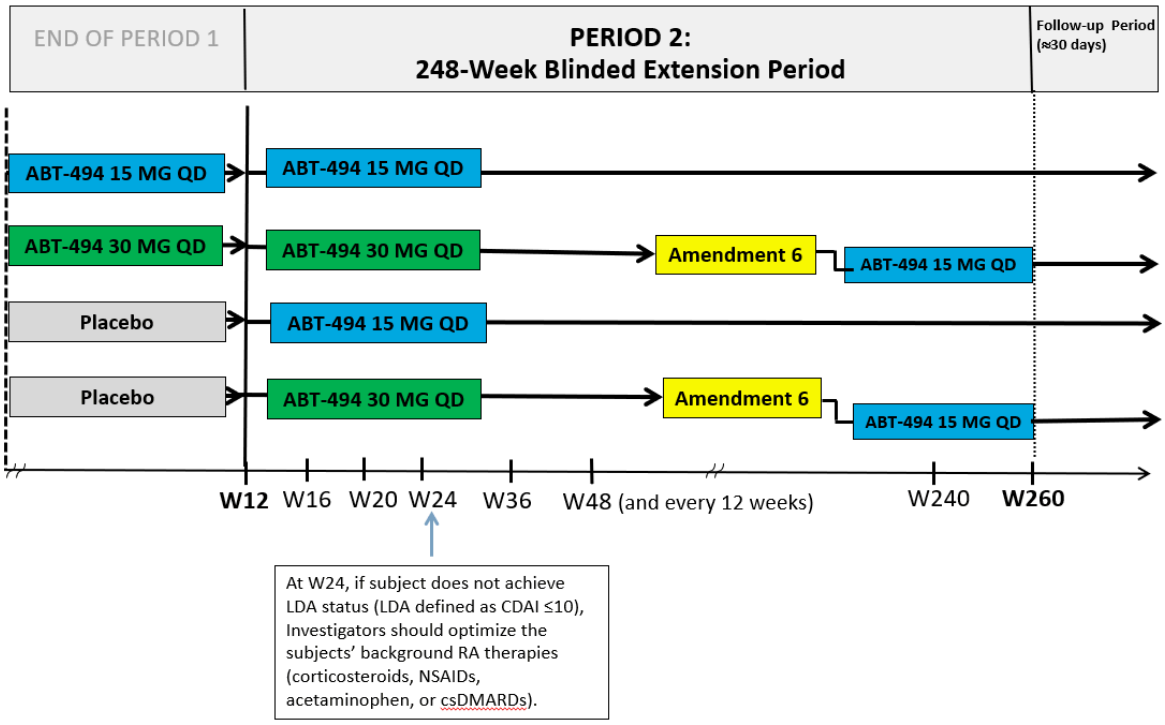
Figure 1. Period 1 Study Design



csDMARD = conventional synthetic disease modifying anti-rheumatic drug; LDA = low disease activity; QD = once daily; RA = rheumatoid arthritis

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

Figure 2. Period 2 Study Design



csDMARD = conventional synthetic disease modifying anti-rheumatic drug; QD = once daily; W = week

Note: Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

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 previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

Subjects that initially screen fail (for reasons other than laboratory values) for the study are permitted to re-screen once following re-consent. 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), or 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 (12-Week Randomized, Double-Blind Treatment Period)

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 12 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 1, 2, 4, 8, and 12. A ± 3 day window is permitted around scheduled study visits. The last dose of study drug in Period 1 is taken the day prior to the Week 12 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 [248 Weeks])

Period 2 will begin at the Week 12 visit after all assessments have been completed. During Period 2, subjects will have a study visit at Weeks 16, 20, 24, 36, 48, every 12 weeks through Week 240 and Week 260/PD. A ± 7 day window is permitted around scheduled study visits. At Week 24, if a subject fails to meet LDA criterion (LDA defined as CDAI ≤ 10) investigator should adjust the subject's background RA therapies.

Starting at Week 24 and thereafter, at least 20% improvement in BOTH TJC AND SJC is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) (see Section 5.2.3.1) must be discontinued from study drug.

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

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 (PD) visit as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy. To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits as outlined in the Study Activities Schedule (Table 4), unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study. As the subject has discontinued study drug, all rescue- and efficacy-driven discontinuation criteria no longer apply. This includes the 20% TJC/SJC calculations at Week 24 and visits thereafter, as well as the CDAI calculation at Week 24, 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 informed 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 and preferably prior to initiation of another therapy. In addition, if the subject is willing, a 30-day follow-up phone call may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs for subjects taking oral study drug.

Follow-Up Period

A Follow-Up Visit will occur approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AE/SAEs, and to collect vital signs and clinical laboratory tests.

Subjects taking oral study drug will complete the 30 day-Follow-Up Visit when they have either:

- Completed the last visit of Period 1 (Week 12), but decided not to participate in Period 2; OR
- Completed the last visit of Period 2; OR
- Prematurely discontinued study drug and/or study participation. If a PD visit has already occurred, then the 30 day Follow-Up visit may be a telephone call if a site visit is not possible. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least one study visit at least 30 days after the last dose of study drug.

Protocol Modifications due to State of Emergency or Pandemic like COVID-19

Study visits may be impacted by a pandemic situation (including the COVID-19 pandemic) or any state of emergency. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others may be performed. Additional details are provided in the subsequent sections. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

5.2 Selection of Study Population

It is anticipated that approximately 600 subjects with moderately to severely active RA will be randomized at approximately 230 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 also fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects have been receiving csDMARD therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug.
    - Subjects must have failed at least one of the following: MTX, sulfasalazine, or leflunomide.
    - Subjects with inadequate response to hydroxychloroquine and/or chloroquine can only be included if they have also failed MTX, sulfasalazine, or leflunomide.
    - The following csDMARDs are allowed (stable dose for ≥ 4 weeks prior to the first dose of study drug): oral or parenteral MTX (15 to 25 mg/week; or

≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 15 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day).

- A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.

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 ≥ 3 mg/L (central lab) at Screening Visit.
5. Stable dose of NSAIDs, acetaminophen, oral corticosteroids (equivalent to prednisone ≤ 10 mg), 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.
6. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of study population). Specifically, prior to enrollment:
   a. Subjects with limited exposure to bDMARD (< 3 months) OR
   b. Subjects who are responding to a bDMARD therapy but had to discontinue due to intolerability (regardless of treatment duration).
7. 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 is specified below or at least five times the mean terminal elimination half-life of a drug:
   - ≥ 4 weeks for etanercept;
   - ≥ 8 weeks for adalimumab, 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.

8. Subjects must have discontinued all high-potency opiates at least 1 week prior to the first dose of study drug (refer to Section 5.2.3.2 for prohibited medications).
9. A negative serum pregnancy test for all female subjects at the Screening Visit and a negative urine pregnancy test for all female subjects of childbearing potential at baseline prior to the first dose of study drug.
10. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
11. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 90 days after the last dose of study drug, to practice the protocol-specified contraception (refer to Section 5.2.4).
12. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

Criteria	Rationale
1 – 8	To select the appropriate subject population
9 – 11	The effect of upadacitinib on pregnancy and reproduction is unknown
12	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 are considered inadequate responders to bDMARD therapy as determined by the Investigator.
3. History 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 30 days after the last dose of study drug.
7. Male who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug.
8. Any active or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or known history of human immunodeficiency virus (HIV). Active HBV and HCV 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);

- HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).

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 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 or a history of associated gastrointestinal diseases including but not limited to diverticulitis and gastroduodenal ulcers.
15. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome.
16. Subject has been a previous recipient of an organ transplant.
17. 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.
18. 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.
19. History of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

20. 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/1.73 m^2;
    - Total white blood cell (WBC) count < 2,500/µL;
    - Absolute neutrophil count (ANC) < 1,500/µL;
    - Platelet count < 100,000/µL;
    - Absolute lymphocyte count < 850/µL;
    - Hemoglobin < 10 g/dL.
21. History of 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, or uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg, or any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.
22. Clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec (males) or > 470 msec (females).

Rationale for Exclusion Criteria

Criteria	Rationale
1 – 3	To select the appropriate subject population
6, 7	The impact of upadacitinib on pregnancies is unknown
4, 5, 8 – 22	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.

The AbbVie Therapeutic Area Medical Director 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 csDMARD 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 ≥ 15 mg/week], sulfasalazine [≤ 3000 mg/day], hydroxychloroquine [≤ 400 mg/day], chloroquine [≤ 250 mg/day], and leflunomide [≤ 20 mg/day]) up to Week 24. At any time, the csDMARD dose may be decreased only for safety reasons. Subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent, such as folinic acid) throughout study participation. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions. AbbVie will not provide the csDMARDs (or folic acid, if taking MTX).

Subjects should 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 (specific time period or protocol-defined rescue);
- 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.

At Week 24 (after Week 24 assessments have been performed), if a subject fails to meet the LDA criterion (LDA defined as CDAI ≤ 10), the investigator should adjust the subject's background RA therapies. Initiation of or change in corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses of csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 3) is allowed as per local label. Starting at Week 24 and thereafter, 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. Also, per investigator's judgment background RA therapies (corticosteroids, NSAIDS, acetaminophen, csDMARDs) can be adjusted for each subject beyond Week 24 until end of Period 2. 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.

5.2.3.2 Prohibited Therapy

JAK Inhibitor

Prior exposure to JAK inhibitors and concurrent use during the study (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 during the first 24 weeks of the study. Intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids are NOT allowed up to Week 24.

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 for RA may be enrolled in the study (up to 20% of study 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).

Subjects must have discontinued the bDMARD prior to the first dose of study drug as specified in the washout procedures (inclusion criterion 7, 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:

- Humira® (adalimumab)
- 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)
- Dupixent® (dupilumab)
- Taltz® (ixekizumab)
- Cosentyx® (secukinumab)
- Entyvio® (vedolizumab)

Strong CYP3A Inhibitors or Inducers

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

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

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

Opiates

High potency opiates are not permitted during the study (i.e., Periods 1 and 2), with the exception of analgesic care related to AEs or SAEs 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

Live vaccines are NOT allowed within 4 weeks prior to the first dose of study drug and during Period 1, including at least 30 days (or longer if required locally) after the last dose of 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);
- Zostavax (herpes zoster, live attenuated);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid.

In Period 2, if a live vaccine must be administered during study participation, study drug must be held for at least 30 days prior to the vaccination and at least 30 days after the vaccination (or longer if required locally).

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

Administration of inactivated (non-live) vaccines is permitted during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid or biosynthetic, include but are not limited to: injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted) and, pertussis (Tdap) vaccines.

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

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

For a female subject at any age:

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

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

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 1 month 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 verbally confirms receipt of medical assessment of the surgical success and is the only sexual partner.
- 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 therapy upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant csDMARD and that duration of contraception after discontinuation of the csDMARD should be based on the local label. Additional local requirements may apply. Refer to Appendix O for local requirements for Canada and Korea.

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.

Contraception Recommendation for Males

There are no contraception requirements for upadacitinib for male subjects or their female partner(s).

Contraception recommendations related to use of background csDMARDs including MTX, as well as concomitant therapies prescribed per standard of care, should be based on the local label.

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.

Study visits may be impacted by state of emergency or pandemic situations like COVID-19. This may include changes such as virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in Section 5.3.1.1.

Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Supplemental study case report forms should be completed in the event of missed/virtual visits, or study drug interruptions or discontinuations related to COVID-19.

Study Visits and/or activities should be performed as scheduled whenever possible. During a state of emergency or pandemic situation, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, study visits may be conducted in a subject's home residence (see Section 5.3.1.1 – Sub-Section "Optional Home Healthcare Service Due to State of Emergency or Pandemic Situation like COVID-19").
- The following study activities may be performed virtually by phone/video conference:
  - Adverse event assessment
  - Concomitant therapy assessment including compliance to contraception requirements, if applicable

- Latent TB risk assessment
- Communication of in-home urine pregnancy test result
- Dispense study drug and subject dosing diary (see Section 5.3.1.1 - Sub-Section "Study Drug Dispensing, Dosing, and Compliance" for details about the Direct-to-Patient shipment)
- Review of subject dosing diary, compliance to IP administrations

- During a virtual visit, the following activities should not be performed:
  - Patient questionnaires
  - X-rays (bilateral hands/feet)
  - Vital signs and body weight
  - Physical exam
  - Physician Global Assessment (PhGA)
  - TJC68/SJC66
- The following study activities may be performed by a local clinic/hospital/laboratory:
  - QuantiFERON-TB Gold test or equivalent (and/or local PPD skin test)
  - Chest x-ray, if the Investigator has determined, based on clinical judgement, that a CXR is required to ensure that it is safe to continue study drug administration (e.g., subjects with seroconversion on an annual TB test).

    In this case, CXR should be performed as soon as restrictions allow at the study site or local hospital/facility. Otherwise, the CXR will be performed at the next earliest feasible visit.
  - 12-lead ECG, if the Investigator has determined, based on clinical judgement, that an ECG is required to ensure that it is safe to continue study drug administration. In this case, ECG should be performed as soon as restrictions allow at the study site or local hospital/facility. Otherwise, the ECG will be performed at the next earliest feasible visit.
  - Local urine pregnancy test
  - Lab tests (blood chemistry, hematology, urinalysis)
  - ESR

All procedures performed at local facilities must be performed by appropriately qualified personnel.

- Lab draws should be obtained as close as possible to the scheduled visit.
- The study site should keep records of all visits/study activities performed virtually by phone/video or through the optional Home Healthcare Service or by a local clinic/hospital/laboratory.

Table 2. Study Activities (Period 1)

Activity	Screening D –35 to D –1	BL D1[b]	Wk 1 D8	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12/ PD[a] D85	30-Day F/U Visit[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
Prior/concomitant therapy	X	X	X	X	X	X	X	X
Patient questionnaires[g] PtGA Pain (VAS) HAQ-DI Morning Stiffness (severity and duration)		X	X	X	X	X	X	
Patient questionnaires[g] EQ-5D-5L SF-36 FACIT-F RA-WIS		X			X		X	
Latent TB risk assessment form[h]	X							
Central lab QuantiFERON-TB Gold test[h] (and/or local PPD skin test)	X							

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

Activity	Screening D –35 to D –1	BL D1[b]	Wk 1 D8	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12/ PD[a] D85	30-Day F/U Visit[c]
Chest x-ray[i]	X							
12-lead ECG[j]	X						X	
Height (screening only) and weight	X	X		X	X	X	X	X
Vital signs[k]	X	X		X	X	X	X	X
Physical exam[l]	X	X					X	
Physician Global Assessment (PhGA)		X	X	X	X	X	X	
TJC68/SJC66	X	X	X	X	X	X	X	
Serum pregnancy test at central lab[m]	X							
Local urine pregnancy test[n]		X		X	X	X	X	X
Central lab tests hsCRP[o] Blood chemistry[p] Hematology (CBC) Urinalysis[q]	X	X	X (hsCRP only)	X	X	X	X	X
ESR (local lab)	X	X	X	X	X	X	X	
Other central lab tests Rheumatoid factor Anti-CCP autoantibodies HBV/HCV screening	X							

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

Activity	Screening D –35 to D –1	BL D1[b]	Wk 1 D8	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12/ PD[a] D85	30-Day F/U Visit[c]
HIV local lab (if required)[r]	X[r]							
IgG and IgM (central lab)		X				X		
Blood samples for upadacitinib PK assay			X[s]	X[s]	X[t]	X[t]	X[t]	
In vivo pharmacodynamic biomarkers		X				X	X	X
Blood samples for exploratory research and validation studies (optional – see Table 3)[u]		X		X	X		X	
Randomization/Drug assignment		X						
Dispense study drug and subject dosing diary		X			X	X	X[v]	
Review and copy subject dosing diary and perform drug reconciliation					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 prematurely discontinues 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 which will be obtained at Screening only and used as the baseline reference.

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 PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

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. Prior to other procedures. For morning stiffness, duration will be captured only if NRS rating is > 0.

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

i. The 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).

j. 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.

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

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

m. For all females, collect serum for pregnancy test only at screening. If serum pregnancy test comes back borderline, a repeat test is necessary (pregnancy is an exclusion criterion). Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.

n. For all women of childbearing potential, collect urine for pregnancy test at Baseline and all subsequent visits except Week 1. 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.

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

p. 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.

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

r. If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to HIV at Screening, and it should be documented that the test has been performed. This testing is to be done at a local 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.

s. At Week 1 and Week 2 visits, PK samples should be collected prior to dosing and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample should be collected at any time during the visit.

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

u. Samples only collected if subject provides written consent.

v. For subjects entering Period 2.

Note: Visit window is ± 3 days for 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 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.

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/PD D85
Pharmacogenetic samples[a,b]	--	X	--	--	--	--
Epigenetic samples[b]	--	X	X	X	--	X
Transcriptomic and epigenetic samples[b]	--	X	X	X	--	X
Plasma samples for proteomic and targeted protein investigations[b]	--	X	X	X	--	X
Serum samples for proteomic and targeted protein investigations[b]	--	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.

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 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks[a]	Every 24 Weeks[a]	Every 48 Weeks[a]	Final/ (Wk 260)/ PD Visit	30-Day F/U Visit[b]
Adverse event assessment	X	X	X	X	X		X			X	X
Concomitant therapy	X	X	X[c]	X	X		X			X	X
Patient questionnaires[d] PtGA Pain (VAS) HAQ-DI Morning Stiffness (severity and duration)	X	X	X	X	X		X			X	
Patient questionnaires[d] EQ-5D-5L SF-36 FACIT-F RA-WIS			X		X						
Latent TB risk assessment form					X				X		
Central lab QuantiFERON-TB Gold test[e] (and/or local PPD skin test)					X[e]				X[e]		
Chest x-ray[f]					X[f]				X[f]		
12-lead ECG[g]					X[g]				X[g]	X	

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

Activity	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks[a]	Every 24 Weeks[a]	Every 48 Weeks[a]	Final/ (Wk 260)/ PD Visit	30-Day F/U Visit[b]
Vital signs and body weight[h]	X	X	X	X	X		X			X	X
Physical exam[i]			X		X			X		X	
Physician Global Assessment (PhGA)	X	X	X	X	X		X			X	
TJC68/SJC66	X	X	X	X	X		X			X	
20% joint assessment (TJC and SJC)[j]			X	X	X		X				
CDAI IRT calculation[k]			X								
Local urine pregnancy test[l]	X	X	X	X	X		X			X	X
In-home urine pregnancy test[m]						X					
Central lab tests hsCRP[n] Blood chemistry[o] Hematology (CBC) Urinalysis[p]	X	X	X	X	X		X			X	X
ESR (local lab)	X	X	X	X	X		X			X	

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

Activity	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks[a]	Every 24 Weeks[a]	Every 48 Weeks[a]	Final/ (Wk 260)/ PD Visit	30-Day F/U Visit[b]
In vivo pharmacodynamic biomarkers	X		X	X	X			X			X
Dispense study drug and subject dosing diary	X	X	X	X	X		X				
Review and copy subject dosing diary and perform drug reconciliation	X	X	X	X	X		X			X	

BL = Baseline Visit; 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, or 48 weeks from the Week 48 visit through Week 240.

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

c. At Week 24 (after Week 24 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).

d. Prior to other procedures. For morning stiffness, duration will be captured only if NRS rating is > 0.

e. TB testing should be performed every 48 weeks after Week 48 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. Study drug should not be withheld at the time of prophylactic treatment (refer to Section 5.3.1.1).

f. Starting at Week 48 obtain chest x-ray every 48 weeks 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.

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

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

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 48. A symptom-directed physical exam may be performed when necessary.

j. Starting at Week 24 and thereafter, 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.

k. CDAI calculation requires input of SJC28 + TJC28 + PtGA + PhGA into IRT system. At Week 24, investigator should optimize background RA therapies in subjects who failed to achieve CDAI ≤ 10.

l. 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.

m. Starting at Week 24, for women of childbearing potential, in-home urine pregnancy tests will be performed monthly.

n. Results of hsCRP may unblind the treatment assignment, and the results may be blunted in subjects taking a JAK inhibitor, thereby limiting its clinical utility in the setting of a possible safety assessment or adverse event management. Therefore, any local testing of hsCRP or CRP is strongly discouraged. In Period 2, the central lab hsCRP results will remain blinded to Investigator, study site personnel, and the subject. Starting with Amendment 6, at a timepoint specified by the Sponsor in Period 2, central laboratory hsCRP results will be reported to the Investigator/study site personnel. After treatment assignment is unblinded, local hsCRP or CRP tests are allowed.

o. 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.

p. 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.

Note: Visit window is ± 7 days for the study. 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 PD visit as soon as possible, preferably within 2 weeks. Refer to Section 5.1 Discontinuation of Study Drug and Continuation of Study Participation for additional details.

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 in vivo pharmacodynamic biomarkers (discussed in Section 5.3.1.2.1), exploratory research and validation studies (discussed in Section 5.3.1.2.2), 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 F)
- Patient's Assessment of Pain Visual Analog Scale (VAS) (Appendix G)
- Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess the physical function and health-related quality of life of each subject (Appendix H)
- Patient's Assessment of Severity and Duration of Morning Stiffness Numerical Rating Scale (NRS) (Appendix I)*
- EuroQoL-5D-5L (EQ-5D-5L) (Appendix J)
- Short Form-36 (SF-36) (Appendix K)
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (Appendix L)
- Work Instability Scale for RA (RA-WIS) (Appendix M)

Period 2

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

- Patient's Assessment of Pain Visual Analog Scale (VAS) (Appendix G)
- Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess the physical function and health-related quality of life of each subject (Appendix H)
- Patient's Assessment of Severity and Duration of Morning Stiffness Numerical Rating Scale (NRS) (Appendix I)*
- EuroQoL-5D-5L (EQ-5D-5L) (Appendix J) (Weeks 24 and 48 only)
- Short Form-36 (SF-36) (Appendix K) (Weeks 24 and 48 only)
- Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (Appendix L) (Weeks 24 and 48 only)
- Work Instability Scale for RA (RA-WIS) (Appendix M) (Weeks 24 and 48 only)

* 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.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, questionnaires will be completed by the subject at the next feasible visit.

TB Testing/TB Prophylaxis

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 E) 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 the 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 TB Skin Test should be considered positive with no requirement for subsequent testing with either PPD or QuantiFERON-TB Gold Plus.

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.

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. If a site has the capacity to perform both PPD and QuantiFERON-TB Gold tests, and local guidelines require only one test to be performed, then the QuantiFERON-TB Gold is the preferred test. At a site with capacity to perform both tests, whatever TB test method (i.e., PPD or QuantiFERON TB Gold or other IGRA) was performed at screening, then the subject should have their annual TB test performed with the same test method.

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.

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.

At Screening, if the subject has evidence of 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 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 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

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 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.

For subjects with seroconversion on an annual TB test, if a CXR cannot be done due to state of emergency or pandemic situation like COVID-19, the Investigator should contact the AbbVie TA MD to determine if the subject may continue on study drug. CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

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 local testing result is negative, then the patient is considered to be negative. 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) of latent TB or active TB (as applicable).

- Interpretation of a positive annual TB test in low risk subjects: In cases where the QuantiFERON-TB Gold Plus test by the central laboratory is positive and the Investigator considers the subject at low risk for TB and has no clinical suspicion of TB, the Investigator may perform a local QuantiFERON-TB Gold Plus test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the Investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive or indeterminate, the test is considered positive.
- An equivalent Interferon Gamma Release Assay (IGRA) (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold Plus.

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

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. 2 to 4 weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms as well as laboratory assessment of toxicity to TB prophylaxis.

Newly initiated prophylactic treatment and prior therapy should be captured in the eCRF.

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.

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.
- Every 48 weeks for subjects with newly identified TB risk factors as determined by the TB risk assessment form (Appendix E), or for subjects living in areas endemic for TB or for subjects with newly positive PPD and/or QuantiFERON-TB Gold test.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, if a visit requires completion of a CXR, the CXR will be performed at the next earliest feasible visit, unless the Investigator has determined, based on clinical judgement, that a CXR is required to ensure that it is safe to continue study drug administration. In this case, CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

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.

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. A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. In cases of QTcF prolongation, 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.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, if a visit requires completion of an ECG, the ECG will be performed at the next earliest feasible visit, unless the Investigator has determined, based on clinical judgement, that an ECG is required to ensure that it is safe to continue study drug administration. In this case, the ECG should be performed as soon as restrictions allow at the study site or local hospital/facility.

Height and Weight

Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits except Week 1 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.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, if a visit by phone or video conference occurs at one of the designated study visits specified to complete physical examination, the complete physical examination will be performed at the next feasible visit.

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

Physician Global Assessment of Disease Activity 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 C).

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, the Physician Global Assessment of Disease Activity will be completed by the physician at the next feasible visit.

TJC and SJC Assessment

TJC Assessment

An assessment of 68 joints (Appendix D) 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 D) 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.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, the TJC and SJC will be performed at the next feasible visit by the independent joint assessor, if possible.

CDAI

The CDAI calculation is required to determine if a subject fails to achieve low disease activity at the Week 24 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 24 is as follows:

$$\text{CDAI} = \text{TJC28} + \text{SJC28} + \text{PtGA (cm)} + \text{PhGA (cm)}$$

NOTE: Investigator should optimize background RA therapies in subjects who failed to achieve a CDAI ≤ 10.

Pregnancy Test

A serum pregnancy test will be performed for all female subjects 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 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, the AbbVie Therapeutic Area Medical Director needs to be consulted.

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 all subsequent visits except Week 1. 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 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 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 positive, study drug must be permanently discontinued.

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

In the event a urine pregnancy test may not be performed at the protocol specified visits due to study modifications related to a state of emergency or pandemic situation like COVID-19, it can be performed by subjects at a local laboratory or it is possible for the Investigator to arrange a shipment from the study site directly to the subject's home of urine pregnancy test kits to have the urine pregnancy test done at home (see Section 5.3.1.1 - Sub-Section "Study Drug Dispensing, Dosing, and Compliance" for details). Home urine pregnancy test should be performed monthly, regardless of ability to obtain other laboratory samples.

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

If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation as described in Section 5.2.4 is available, pregnancy testing is no longer required.

A pregnant or breastfeeding female will not be eligible for participation or continuation on 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.

If travel restrictions or other changes in local regulations due to state of emergency or pandemic situation like COVID-19 prevent the subject from having blood drawn for laboratory testing at the study site, it is possible for the Investigator to arrange for subjects to have laboratory work done at a local lab, hospital, or other facility to ensure the safety assessments are conducted per protocol. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator or designee as soon as possible and documented in the eCRF.

If laboratory samples cannot be obtained, study drug administration may be continued provided labs have been obtained within the prior 3 months, the investigator has reviewed the laboratory results and confirmed and discussed with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current lab results. The subject should be scheduled for laboratory draws as soon as feasible and no later than the next scheduled visit in order to continue the study drug administration.

If laboratory results are not available within the prior 3 months/two consecutive 12-week intervals, study drug dispensation is not allowed until the required laboratory tests are completed to ensure the safety assessments are conducted per protocol.

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.

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	<u>Central Lab Tests:</u> Serum pregnancy (bHCG) test[d] HBs Ag[e] HBs Ab[e] HBc Ab[e] HBV DNA PCR[e] HCV Ab[e] HCV RNA (reflex only)[e] QuantiFERON-TB Gold[f] Rheumatoid Factor[e] Anti-CCP autoantibodies[e] hs-CRP[g] IgG and IgM FSH[h] <u>Local Lab Tests:</u> Urine pregnancy test[i] ESR HIV (if required)[j]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bHCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CCP = cyclic citrullinated peptide; 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; 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.

c. INR will only be measured with a separate blood sample at repeat testing if ALT and/or AST > 3 × ULN.

Table 5. Clinical Laboratory Tests (Continued)

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. HBV DNA testing is required for subjects who meet specific toxicity management criteria (See ALT/AST toxicity management criteria in Table 7).
f. If PPD not performed.
g. In Period 1, the central lab hsCRP results starting from Baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, and the subject. Results of hsCRP may unblind the treatment assignment, and the results may be blunted in subjects taking a JAK inhibitor, thereby limiting its clinical utility in the setting of a possible safety assessment or adverse event management. Therefore, any local testing of hsCRP or CRP is strongly discouraged. In Period 2, the central lab hsCRP results will remain blinded to Investigator, study site personnel, and the subject. Starting with Amendment 6, at a timepoint specified by the Sponsor in Period 2, central laboratory hsCRP results will be reported to the Investigator/study site personnel. After treatment assignment is unblinded, local hsCRP or CRP tests are allowed.
h. At screening for female subjects < 55 years old.
i. A urine pregnancy test will be performed for all women of childbearing potential at the Baseline Visit prior to the first dose of study drug and all subsequent visits except Week 1. 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. 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.
j. If required by country regulatory authorities to confirm eligibility, subjects will be tested for antibodies to HIV at Screening, and it should be documented that the test has been performed. This testing is to be done at a local 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.

Hepatitis Screen

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

Hepatitis B Virus (HBV):

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

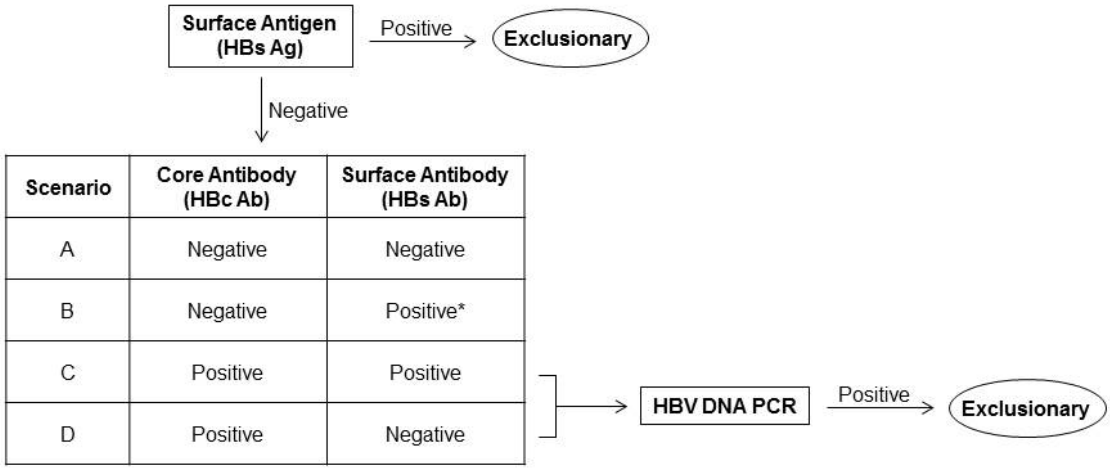
- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

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 3, 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 3, Scenario B).*
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 3, 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 3. Criteria for HBV DNA PCR Qualitative Testing



* For subjects who have had a HBV vaccination (should document 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 prior to Screening. This testing is to be done at a local 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 2:2:1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: Upadacitinib 30 mg QD (N = 200) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 2: Upadacitinib 15 mg QD (N = 200) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: Placebo (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/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.

Refer to Section 5.5 for additional information.

Study drug may be shipped from the study site directly to the study subject's home due to study modifications related to a state of emergency or pandemic situation like COVID-19 if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Subject agrees to have the study drug shipped directly to their home
- Shipments may also include other study supplies (e.g., drug dosing diaries, in-home urine pregnancy test kits). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to

COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Optional Home Healthcare Service Due to State of Emergency or Pandemic Situation like COVID-19

Subjects may be offered the option of home healthcare visits provided by a study nurse or third-party vendor. Study procedures conducted in the home setting may include vital signs and body weight, physical exam, blood and urine samples collection, urine pregnancy test, adverse event and concomitant therapy assessment including compliance to contraception requirements if applicable, latent TB risk assessment form, review of subject dosing diary, TJC and SJC performed by the same independent joint assessor, if possible, to minimize variability.

This option can only be offered in countries and sites that comply with local regulatory and IRB/IEC requirements for homecare. Any pre-requisite submissions or notifications to the site IRB/IEC and local competent health authority should be made, and approvals must be obtained prior to implementation.

The investigator should be available via phone call if a consultation is necessary.

It is recommended that medical personnel entering a subject's home adhere to local health regulations during the COVID-19 pandemic, such as the use of Personal Protective Equipment (PPE), as required.

If the home visits will not be performed by site personnel, the site may be responsible for selecting a vendor, contracting with a vendor, and for ensuring continued compliance with the terms of the Clinical Study Agreement.

Individuals performing home visits need to be added to the delegation log.

5.3.1.2 Collection and Handling of In Vivo Pharmacodynamic Biomarker and Optional Samples for Exploratory Research and Validation Studies

5.3.1.2.1 In Vivo Pharmacodynamic Biomarker Samples

Blood samples will be collected at the visits indicated in Table 2 and Table 4 and will be utilized to assess effects of upadacitinib inhibition on certain lymphocyte subsets, including but not limited to T (CD4+ and CD8+) cells, B (CD19+) cells, natural killer (NK) cells, and natural killer-T (NKT) cells.

The samples should be labeled and shipped as outlined in the study-specific laboratory manual.

5.3.1.2.2 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. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

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

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

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

- Weeks 1 and 2 prior to dosing;
- Weeks 4, 8, and 12/Premature Discontinuation at any time during the visit.

On Week 1 and Week 2 visit days, if possible, subjects should take the study drug dose at the clinic after collecting the PK blood sample, except if the subjects regularly take the study drug dose at night. Those subjects who regularly take the study drug dose at night should continue to take study drug according to their normal schedule. For all other visits, subjects can take the study drug dose on visit days at their regular schedule and not necessarily at the clinic.

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

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

5.3.2.2 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Period 1 Variables

5.3.3.1.1 Primary Variables

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response (US/FDA regulatory purposes) or the proportion of subjects achieving LDA (EU/EMA regulatory purposes) at Week 12. Analyses will be conducted separately for US/FDA regulatory purposes and EU/EMA regulatory purposes; for each set of analyses, 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.

LDA is defined as DAS28 (CRP) ≤ 3.2. DAS28 (CRP) score will be determined based on a continuous scale of combined measures of TJC, SJC, Patient's Global Assessment of Disease Activity (PtGA) (in mm), and hsCRP (in mg/L) at Week 12.

$$\text{DAS28 (CRP)} = 0.56 \times \sqrt{(\text{TJC28}^{*})} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.36 \times \ln(\text{hsCRP}^{\&} + 1) + 0.014 \times \text{PtGA}^{>>} + 0.96$$

* TJC28 refers to the Subject's total Tender Joint Count out of the provided 28 evaluated joints.

** SJC28 refers to the Subject's total Swollen Joint Count out of the provided 28 evaluated joints.

& hsCRP refers to the high-sensitivity c-reactive protein lab value. hsCRP unit in the DAS28 (CRP) equation is expressed as mg/L.

>> PtGA refers to the Patient's Global Assessment of Disease Activity.

where √ is square root and ln is natural log.

5.3.3.1.2 Key Secondary Variables

Ranked key secondary endpoints (at Week 12) for US/FDA regulatory purposes are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. Change from baseline in SF-36 Physical Component Score (PCS);
4. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2;
5. Proportion of subjects achieving CR based on DAS28 (CRP);
6. Proportion of subjects achieving LDA based on CDAI ≤ 10;
7. Change from baseline in morning stiffness;
8. Change from baseline in FACIT-F.

Ranked key secondary endpoints (at Week 12) for EU/EMA regulatory purposes are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. ACR20 response rate;
4. Change from baseline in SF-36 PCS;
5. Proportion of subjects achieving CR based on DAS28 (CRP);
6. Proportion of subjects achieving LDA based on CDAI ≤ 10;
7. Change from baseline in morning stiffness;
8. Change from baseline in FACIT-F.

Other key secondary endpoints (at Week 12, if not specified) for both US/FDA and EU/EMA regulatory purposes are:

- ACR50 response rate;
- ACR70 response rate;
- ACR20 response rate at Week 1.

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 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;
- Change from baseline in morning stiffness;
- Proportion of subjects achieving MCID in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3);
- Proportion of subjects achieving LDA and proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and CDAI criteria (see below);
- ACR/EULAR Boolean remission;

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

- Change from baseline in EQ-5D-5L;
- Change from baseline in SF-36;

- Change from baseline in FACIT-F;
- Change from baseline in RA-WIS.

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 16, 20, 24, 36, 48, every 12 weeks through Week 240, and Week 260/PD:

- 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 MCID in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ -0.3);
- 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);
- ACR/EULAR Boolean remission;
- Concomitant corticosteroid use (systemic use and intra-articular injections).

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 24 and 48 only:

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

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 In Vivo Pharmacodynamic Biomarker Samples and Exploratory Research Variables and Validation Studies

5.3.6.1 In Vivo Pharmacodynamic Biomarker Samples

Blood samples will be collected to assess the effects of upadacitinib inhibition on lymphocyte subsets including but not limited to: T (CD4+ and CD8+) cells, B (CD19+) cells, NK cells, and NKT cells.

5.3.6.2 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 participation 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 be withdrawn from study drug treatment 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 significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial as determined by the Investigator.
- Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injuries).
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.
- Starting at Week 24, at least 20% improvement in BOTH SJC AND TJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) must be discontinued from study drug.

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, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent). 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 drug treatment and 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 phone call after the last dose of study drug may be completed to ensure all treatment emergent AEs/SAEs have been resolved. Subjects who discontinue the study prematurely after randomization will not be replaced.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the Investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

During the COVID 19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care.

During a state of emergency or pandemic situation like COVID-19, the investigator should contact the sponsor medical contact before discontinuing a subject from the study or study drug for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Lost to Follow-Up

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

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately

notify the Investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be taken orally 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 csDMARD. AbbVie will not supply csDMARD(s) (nor folic acid or equivalent, such as folinic acid, for subjects who are on MTX).

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

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 30 mg	AbbVie
Matching placebo	Oral	Tablet	NA	AbbVie

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.

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

- Group 1: Upadacitinib (ABT-494) 30 mg QD (N = 200) (Period 1) → Upadacitinib (ABT-494) 30 mg QD (Period 2)
- Group 2: Upadacitinib (ABT-494) 15 mg QD (N = 200) (Period 1) → Upadacitinib (ABT-494) 15 mg QD (Period 2)
- Group 3: Placebo (N = 100) (Period 1) → Upadacitinib (ABT-494) 30 mg QD (Period 2)
- Group 4: Placebo (N = 100) (Period 1) → Upadacitinib (ABT-494) 15 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/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.

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

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 1 and Week 2 visits).

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

If a subject should forget to take their upadacitinib (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 > 7 consecutive days

during Weeks 1 through 24 or > 30 consecutive days after Week 24, they should notify their Investigator, and the Investigator will determine if study drug should be restarted.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the Investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

In order to maintain the blind, the upadacitinib (ABT-494) tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of medical emergency.

In the event of a medical situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie 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.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study.

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD. Study sites and subjects will no longer be blinded after this point.

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.

As of September 2018, with all subjects having reached the end of Period 1, and after final review of unblinded safety data, the DMC concluded its oversight of this study.

5.5.6 Treatment Compliance

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

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

5.5.7 Drug Accountability

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

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

All empty/used study drug packaging will be inventoried by the site. 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. Site staff will complete study drug accountability via IRT, by using source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible. After drug accountability and monitor reconciliation 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 (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.

Monitors will reconcile the site's processes, source documents, subject's dosing diaries, IRT or site accountability records, and destruction records to assure site compliance.

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 12-week, randomized, double-blind, placebo-controlled period to compare safety and efficacy of upadacitinib versus placebo in subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 1 is designed to test superiority of upadacitinib versus placebo for achieving the primary endpoint (ACR20 for US/FDA regulatory purposes or LDA for EU/EMA regulatory purposes) at Week 12, and other secondary efficacy parameters, all on a stable background csDMARD therapy.

The purpose of Period 2 is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 30 mg QD and 15 mg QD in a blinded fashion in subjects with RA who have completed Period 1. Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 15 mg or 30 mg QD in a blinded fashion per pre-specified randomization assignments. Preventing dose reduction or escalation of upadacitinib during Period 2 will allow better assessments of long-term safety and efficacy of upadacitinib 15 mg QD versus 30 mg QD.

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

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 csDMARD 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 ≥ 3 mg/L (central lab) at Screening. Subjects must have been on a stable dose of csDMARD therapy (restricted to MTX, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug. Subjects with inadequate response to hydroxychloroquine and/or chloroquine can only be included if they also failed MTX, sulfasalazine, or leflunomide.

5.6.4 Selection of Doses in the Study

Two doses of the once-daily formulation of upadacitinib will be evaluated: upadacitinib 15 mg QD and 30 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 doses selected for Study M13-549, upadacitinib 15 mg QD and 30 mg QD, dosed for up to 260 weeks, are expected to be efficacious with an acceptable safety profile.

Doses of 15 mg QD and 30 mg QD using the once-daily formulation provide equivalent daily AUC and comparable C_{max} and C_{min} to 6 mg BID and 12 mg BID, respectively, 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 and the 12 mg BID dose was clearly shown to achieve the plateau of 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.

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;
- Active tuberculosis;
- Malignancy (all types);
- Adjudicated Gastrointestinal perforations;

- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Anemia;
- Neutropenia;
- Lymphopenia;
- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Increased creatine phosphokinase (CPK);
- Adjudicated embolic and thrombotic events (non-cardiac, non-CNS).

6.1.2 Adverse Event Severity

The investigator will classify AEs according to the Rheumatology Common Toxicity Criteria v.2.0 (Appendix N).[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 relationship or deemed it not assessable, AbbVie will consider the event associated.

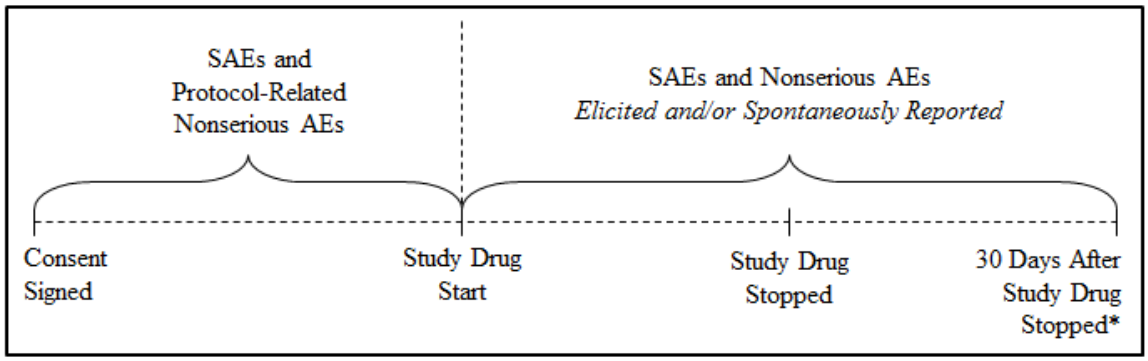
If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

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

Adverse event information will be collected as shown in Figure 4.

Figure 4. Adverse Event Collection



* Subjects who discontinue study drug but continue to participate in the study will have SAEs and Non serious AEs collected for the remainder of study participation.

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

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

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures (SAE Supplemental Procedure eCRF)
- Embolic and thrombotic events (non-cardiac, non-CNS).
- Hepatic;
- Renal;
- Herpes Zoster Infection;
- CPK increases considered by the investigator to be an AE;
- COVID-19

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including documentation of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above.

The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID-19 Supplemental Signs/ Symptoms

- COVID-19 Status Form

6.1.5 Serious Adverse Event Reporting

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

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064

Toll Free: +1 (833) 942-2226
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

Primary Therapeutic Area Medical Director:

[redacted] MD
Medical Director
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office:
Mobile:
Fax:
Email: [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: +1 (973) 784-6402

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.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes 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 and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. Refer to Appendix O for local requirements for Canada. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

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 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 7 consecutive days during the first 24 weeks 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.

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The COVID-19 eCRF must be completed.

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

Gastrointestinal Perforation: If a diagnosis of gastrointestinal perforation is confirmed (other than appendicitis or penetrating injury), the subject must be permanently discontinued from study drug.

Cardiovascular Events (MACE): 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.

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

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

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 are described in Table 7 and may require an appropriate supplemental eCRF to 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 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 cells/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 cells/µL by repeat testing with new sample.
Absolute lymphocyte counts (ALC)	• If confirmed < 500 cells/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 cells/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 cells/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 (INR) > 1.5. ○ 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. • If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD. 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. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. • For 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 one week: ○ ALT > 5 × ULN OR ○ ALT or AST > 3 × ULN if an alternative cause is not readily identified. ○ 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 one week for recommendation regarding subsequent treatment. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.
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.

Table 7. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
Creatine Phosphokinase	• If confirmed CPK value ≥ 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

- Allow study drug interruption up to 7 consecutive days for AEs and emergency surgery. Elective surgery will not be allowed during this 12 week-period.
- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Period 2

- Allow study drug interruption up to 7 consecutive days for AEs and emergency surgery up until the Week 24 visit in Period 2, and after Week 24 and thereafter, up to 30 consecutive days of study drug interruption is allowed. The Investigator will make determination if study drug should be restarted for interruptions > 30 days.
- Elective surgery is allowed starting at Week 24 in Period 2. If the subject undergoes elective surgery, the study drug should be interrupted 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of surgery. Allow reintroduction of study drug once the

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

6.1.8 Data Monitoring Committee

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

6.1.9 Cardiovascular Adjudication Committee

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

6.2 Product Complaint

6.2.1 Definition

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

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (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 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product

Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. 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, including those that may be due to the COVID-19 or any pandemic or any state of emergency situation) 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:

[redacted]
Study Project Manager I
AbbVie S.r.l.
Viale dell'Arte, 25
00144 Roma

Office: [redacted]
Fax:
Email:

Alternate Contact:

[redacted]
Study Management Associate III
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email:

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

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

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study.

Completed and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock for the analysis at the end of Period 1. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

Starting with Amendment 6, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD. The details for handling the change in dose in analysis will be described in the Statistical Analysis Plan (SAP) for final reporting.

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. The exposure to study drug is defined as the difference between the dates of the first and last doses of the study drug plus 1 day.

Study drug compliance will be summarized for each treatment group 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.

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

For all efficacy analysis in Period 1, the two placebo groups (Groups 3 and 4) will be combined and treated as one placebo group for analysis purposes. Each upadacitinib dose will be compared with the combined placebo group.

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 analyses, only one primary endpoint is specified.

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

The primary efficacy analyses will also be performed in demographic subgroups including age, gender, 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 (at Week 12) for US/FDA regulatory purposes are listed in Section 5.3.3.1.2. Key secondary endpoints in (at Week 12) for EU/EMA regulatory purposes are also listed in Section 5.3.3.1.2.

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

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons for each of the upadacitinib treatment groups and the combined placebo groups 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.

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. 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 Key Ranked Secondary Endpoints

The overall type I error rate of the primary and ranked key secondary endpoints for the two doses will be strongly controlled using a graphical multiple testing procedure.[23]

Specifically, the testing will utilize the endpoint sequence of primary endpoint followed by the ranked key secondary endpoints, and will begin with testing the primary endpoint using α of 0.025 for each dose. Continued testing will follow a pre-specified α transfer path which includes downstream transfer along the endpoint sequence within each dose as well as cross-dose transfer. More details of the graphical procedure will be specified in the SAP.

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 imputes missing data multiple times under appropriate random variation and thus generates 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.

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. Sensitivity analyses based on OC will also be conducted for key endpoints.

8.1.4.2 Long-Term Efficacy Analysis 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 Period 1 alone, as well as for Period 1 and Period 2 combined.

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 the Period 1 safety analysis and the combined safety analysis of Period 1 and Period 2.

8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)

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

AEs starting more than 30 days following the last dose of study drug will not be included in summaries of TEAEs. For subjects who continued into Period 2, AEs that are reported in Period 2 will be captured in the combined safety analysis of Period 1 and Period 2.

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, 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.

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 creatinine, 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 level.

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

8.1.6 Pharmacokinetic and Exposure-Response Analyses

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

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

Population PK analyses will be performed using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling 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 will be performed if useful and appropriate.

8.1.7 Statistical Analysis of Biomarker Data

Summary statistics for the in vivo pharmacodynamic biomarkers (including but not limited to NK, NKT, B cells, and T cells) at baseline and post-treatment time points (Weeks 8 and 12/PD in Period 1, and Weeks 16, 24, 36, 48 and every 24 weeks thereafter in Period 2), in addition to change from baseline at each time will be provided; this will include mean, standard deviation, median, quartiles, and range for each group. The pharmacodynamic effect of each biomarker between the placebo and upadacitinib treatment groups will be evaluated via a non-linear mixed-effects modeling approach with Change from baseline of the biomarker as response variable, Treatment, Time, and Treatment × Time interaction as fixed-effects, the corresponding baseline biomarker score as a covariate, and "subjects nested within the treatment group" as a random-effect. Other baseline variables such as age, weight, etc., may be considered as appropriate. For biomarkers identified to have significant overall treatment effect via the non-linear mixed-effects modeling analysis, dose-response models with the biomarker as a continuous response will be explored. In addition to the above analyses of biomarkers

individually, the effect of certain combination of biomarkers on the treatment groups may be explored.

If the optional exploratory research variables including an additional panel of prognostic, predictive, and pharmacodynamic biomarkers are evaluated, then those data may be analyzed as follows. The association of biomarkers to the efficacy and safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling algorithms. Optimal multivariate combinations of biomarkers that associate with efficacy endpoints, subject response/non-response (with respect to appropriate clinical endpoints), and also with safety endpoints may be explored via a variety of statistical predictive modeling algorithms. Also cut-points for individual biomarkers and optimal combinations of biomarkers that differentiate the subject response with respect to efficacy/safety endpoints may be explored. The significance of these multivariate combinations of biomarkers may be assessed via at least 20 iterations of 5 fold cross-validation.

8.2 Determination of Sample Size

The planned total sample size of 600 for this study provides at least 90% power for a 21% difference in ACR20 response rate (assuming a placebo ACR20 response rate of [redacted]), as well as at least 90% power for a 22% difference in LDA response rate (based on DAS 28 [CRP] [assuming a placebo LDA response rate of [redacted]]), at two sided significance level of 0.025 and accounting for a 10% dropout rate. This sample size will also provide at least 90% power for most of the key secondary endpoints, including change from baseline in DAS28(CRP), change from baseline in HAQ-DI, ACR50 response rate, CR based on DAS28(CRP), and SF-36 PCS, at two-sided significance level of 0.025 and accounting for a 10% dropout rate.

8.3 Randomization Methods

Subjects will be randomly assigned in a 2:2:1:1 ratio to one of the four treatment groups:

- Group 1: Upadacitinib 30 mg QD (N = 200) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 2: Upadacitinib 15 mg QD (N = 200) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: Placebo (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/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.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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.

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

Due pandemic situation like COVID-19 or state of emergency, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

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.

During the COVID-19 pandemic or any pandemic/state of emergency, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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 in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs
Protocol Date:	25 November 2020

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 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]	Executive Medical Director	Immunology Clinical Development
[redacted]	Therapeutic Area Medical Director	Therapeutic Area
[redacted]	Senior Medical Director	Pharmacovigilance and Patient Safety
[redacted]	Senior Director	Statistics
[redacted]	Director Statistics	Statistics
[redacted]	Director, Clinical Pharmacology	Clinical Pharmacokinetics and Pharmacodynamics
[redacted]	Study Project Manager I	Clinical Program Development

Appendix C. 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 D. 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
TOTAL Joint Count												

Appendix E. 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.com/health/tuberculosis/DS00372/DSECTION=risk-factors
http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix F. 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 G. 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 H. 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 yard work?	☐	☐	☐	☐

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

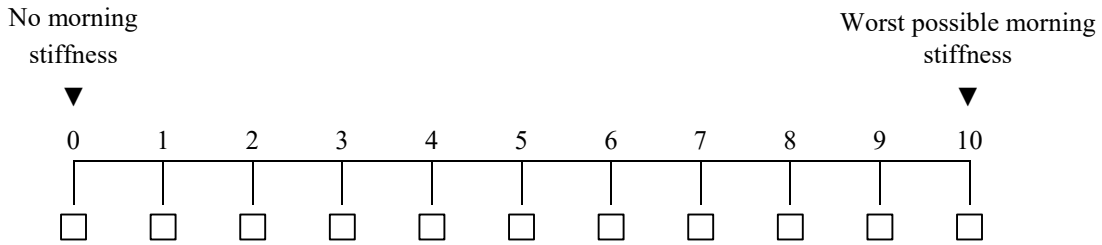
HAQ – United States/English

HAQ-DI_AU1.0-eng-USori.doc

Appendix I. Patient's Assessment of Severity and Duration 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 J. 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

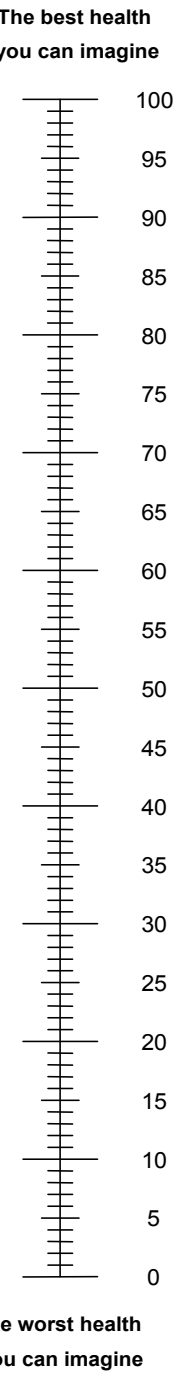
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐

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 K. 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.

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

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

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

Much better now than 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

THANK YOU FOR COMPLETING THESE QUESTIONS

Appendix L. 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.**

		Not at all	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) 16 November 2007

Appendix M. 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 N. 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

G. Gastrointestinal (continued)				
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 (continued)				
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 O_2	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 O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
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 O_2	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 (continued)				
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 = haemoglobin; 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 O. Local Requirements

Canada

Section 5.2.1 Inclusion Criteria

1. 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 30 days after the last dose of study drug.

   Note: The contraception requirement described above is specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant csDMARD and that duration of contraception after discontinuation of the csDMARD (i.e., for methotrexate, contraception is required from Study Day 1 through 180 days after the last dose of methotrexate) should be based on the local label.

2. 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 study drug, to practice the protocol-specified contraception (refer to Section 5.2.4).

   Note: For concomitant csDMARDs, local label should be followed for contraception requirements (i.e., for methotrexate, contraception is required from Study Day 1 through 90 days after the last dose of methotrexate).

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.

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.

- 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 subject 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 two forms** of contraception. This includes one form of highly effective contraception and one effective method of contraception that are effective from Study Day 1 (or earlier) through at least 30 days after the last dose of study drug. For concomitant csDMARDs, the local label should be followed for contraception requirements (i.e., for methotrexate, contraception is required from Study Day 1 through 180 days after the last dose of methotrexate.)

- 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 of become damaged.

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant csDMARD and that duration of contraception after discontinuation of the csDMARD should be based on the local label.

Contraception Recommendation for Males

There are no contraception requirements for male subjects or their female partner(s).

Korea

Section 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 csDMARD therapy (restricted to oral or parenteral MTX [10 to 25 mg/week; or ≥ 7.5 mg/week in subjects who are intolerant of MTX at doses ≥ 10 mg/week; no minimum MTX dose is required if MTX is combined with another csDMARD], sulfasalazine [≤ 3000 mg/day], hydroxychloroquine [≤ 400 mg/day] and leflunomide [≤ 20 mg/day]) up to Week 24.

Section 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 csDMARD 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 ≥ 3 mg/L (central lab) at Screening. Subjects must have been on a stable dose of csDMARD therapy (restricted to MTX, hydroxychloroquine, sulfasalazine, or leflunomide) for

≥ 4 weeks prior to the first dose of study drug. Subjects with inadequate response to hydroxychloroquine can only be included if they also failed (lack of efficacy or intolerability) MTX, sulfasalazine, or leflunomide.

Section 5.2.4 Contraception Requirements

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

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

For a female subject at any age:

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

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

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month 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 therapy upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued

during the study. Contraception should continue while the subject is on the concomitant csDMARD and that duration of contraception after discontinuation of the csDMARD should be based on the local label.

Contraception Recommendation for Males

There are no contraception requirements for male subjects or their female partner(s).