

1.0 Title Page

Clinical Study Protocol M15-555


**A Phase 3, Randomized, Double-Blind Study
Comparing Upadacitinib (ABT-494) Monotherapy to
Methotrexate (MTX) in Subjects with Moderately to
Severely Active Rheumatoid Arthritis with
Inadequate Response to MTX**

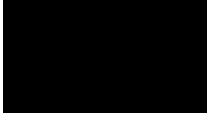

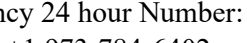
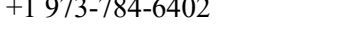
**Incorporating Administrative Changes 1, 2, 3, 5, 7, 8,
9, 10, and 11 and Amendments 1, 2, 2.02, 3, 3.02, 4,
5, 5.02, 6, and 7**

AbbVie Investigational Product:	Upadacitinib	
Date:	04 December 2020	
Development Phase:	3	
Study Design:	A 14-week randomized, double-blind, parallel-group, controlled treatment period followed by a blinded long-term extension period	
EudraCT Number:	2015-003376-75	
Investigators:	Multicenter Trial (Investigator information is on file at AbbVie)	
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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	01 October 2015
Amendment 1	21 January 2016
Amendment 2	29 February 2016
Amendment 2.01 (Japan Only)	09 March 2016
Amendment 2.02 (VHP Countries Only)	27 May 2016
Administrative Change 1	04 March 2016
Administrative Change 2	21 March 2016
Administrative Change 3	12 April 2016
Administrative Change 4 (Japan Only)	13 April 2016
Administrative Change 5	05 May 2016
Administrative Change 6 (Japan Only)	08 June 2016
Amendment 3	06 October 2016
Amendment 3.01 (Japan Only)	02 November 2016
Amendment 3.02 (VHP Only)	04 January 2017
Administrative Change 7 (VHP Only)	20 January 2017
Administrative Change 8	30 March 2017
Amendment 4	25 October 2017
Amendment 4.01 (Japan Only)	15 November 2017
Administrative Change 9	10 January 2018
Amendment 4.01.01 (Japan Only)	18 July 2019
Amendment 5 (Global, except VHP countries and Greece)	13 December 2019
Administrative Change 10	06 January 2020
Administrative Change 11	30 January 2020
Amendment 5.01 (Japan Only)	06 March 2020
Amendment 5.02 (VHP and Greece Only)	10 March 2020
Amendment 6	30 June 2020

The purpose of this amendment is to:

- Apply administrative changes throughout protocol.
Rationale: Revised text to improve consistency and readability, and/or provide clarification.
- Update Cover Page, Medical Emergency Contact
Rationale: Contact information updated with change in Therapeutic Area Medical Director
- Update Section 1.2, Synopsis
Rationale: Revised to be consistent with Amendment 7 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

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- 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. Clarified that the questionnaire *Patient's Assessment of Severity and Duration of Morning Stiffness Numerical Rating Scale* will not be collected starting at Week 276 for consistency with footnote "c." of [Table 4](#) "Study Activities (Period 2)."
 - 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.
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- 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 Primary Therapeutic Area Medical Director contact information to reflect the change in personnel.*
- 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 × 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 9.3, 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:** Updated list of current Protocol Signatories to current.*

1.2 Synopsis

AbbVie Inc.	Protocol Number: M15-555
Name of Study Drug: Upadacitinib	Phase of Development: 3
Name of Active Ingredient: Upadacitinib	Date of Protocol Synopsis: 04 December 2020
Protocol Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX	
Objectives:	
Period 1	
To compare the safety and efficacy (signs and symptoms) of upadacitinib 30 mg once daily (QD) alone and 15 mg QD alone versus continuing methotrexate (MTX) alone in MTX-inadequate response (MTX-IR) subjects with moderately to severely active rheumatoid arthritis (RA).	
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 175	
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 oral or parenteral MTX therapy ≥ 3 months and on a stable dose [15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week] for ≥ 4 weeks prior to the first dose of study drug.	
Number of Subjects to be Enrolled: Approximately 600 subjects	
Methodology:	
This is a Phase 3 multicenter study that includes two periods. Period 1 is a 14-week, randomized, double-blind, parallel-group, controlled treatment period designed to compare the safety and efficacy of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). 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 5 all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.	

Methodology (Continued):

The study duration will include a 35-day screening period; a 14-week randomized, double-blind, parallel-group, controlled treatment period (Period 1); a 246-week blinded extension period (Period 2); and a 30-day follow-up 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 once daily (QD) (N = 200) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 2: Upadacitinib 15 mg once daily (QD) (N = 200) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: MTX (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: MTX (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Each subject will be instructed to take a required number of capsules once weekly (MTX and/or matching placebo) based on prior MTX dose and 1 tablet once daily (upadacitinib or matching placebo) to maintain blinding. MTX and matching placebo will be distributed as active MTX or placebo tablets over-encapsulated into identical capsules in blister packs, to provide the correct total dose for each individual subject and to maintain blinding during Period 1. Detailed dosing instructions can be found in the Subject Dosing Diary and Instructions.

Prior to enrollment, subjects must have been receiving oral or parenteral MTX therapy ≥ 3 months and on a stable dose [15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week] for at least 4 weeks. No MTX washout is needed prior to randomization. All subjects will start on their blinded upadacitinib (30 mg QD, 15 mg QD or Placebo QD) dose at Baseline. Also, starting at Baseline, all subjects will discontinue their current MTX treatment and start their blinded MTX treatment. Subjects will be given oral MTX in a blinded manner (7.5 to 25 mg/week and/or placebo) based on the subject's prior stable dose of MTX. Subjects who are on a stable dose of MTX between 10 and < 15 mg/week at study entry will be assigned to MTX 10 mg/week at randomization. For all other doses of MTX, subjects will be assigned to blinded MTX based on their current stable MTX dose at study entry. In addition, all subjects should take a dietary supplement of folic acid (or equivalent) throughout Period 1 participation; while in Period 2 (starting at Week 26) it should only be taken if MTX is given as background medication. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions.

Subjects who complete the Week 14 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2 (246 weeks). Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 30 mg QD or 15 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to MTX in Period 1 will discontinue MTX and receive upadacitinib 30 mg QD or 15 mg QD in a blinded fashion per pre-specified randomization assignments. Starting with Amendment 5 all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

Methodology (Continued):

At Week 26 (after Week 26 assessments have been performed), subjects who do not achieve LDA as defined by CDAI ≤ 10 should have background medication(s) adjusted or initiated as rescue. Changes to concomitant therapies for RA are allowed as per local label (i.e., initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen, or initiation of csDMARDs [concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide]). Starting at Week 26 and thereafter, study drug will be discontinued for subjects who fail to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits, despite optimization of background RA therapies (see Section 5.2.3.1 for permitted background RA therapies).

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 14). Study sites and subjects will remain blinded for the duration of the study (Period 1 and 2).

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 must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose [15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week] for ≥ 4 weeks prior to first dose of study drug.
4. Must have discontinued all conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (other than MTX; see Inclusion Criterion 3) ≥ 4 weeks prior to first dose of study drug. The washout period for specific csDMARDs prior to first dose of study drug is specified below or should be at least five times the mean terminal elimination half-life of a drug:
 - ≥ 4 weeks for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
 - ≥ 8 weeks for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).
5. 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.

Main Exclusion:

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Prior exposure to any biological disease-modifying anti-rheumatic drugs (bDMARDs).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):	
Main Exclusion (Continued):	
<p>3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial SpA, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms]. Current diagnosis of secondary Sjogren's Syndrome is permitted.</p> <p>4. Laboratory values meeting the following criteria within the Screening Period prior to the first dose of study drug: serum aspartate transaminase > 2 × ULN; serum alanine transaminase > 2 × ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73m²; total white blood cell count < 2,500/μL; absolute neutrophil count < 1,500/μL; platelet count < 100,000/μL; absolute lymphocyte count < 800/μL; and hemoglobin < 10 g/dL.</p>	
Investigational Product:	Upadacitinib
Dose:	30 mg QD 15 mg QD
Mode of Administration:	Oral
Reference Therapy:	<p>Period 1:</p> <ul style="list-style-type: none"> • MTX • Matching placebo for MTX • Matching placebo for upadacitinib <p>Period 2: None</p>
Dose:	<ul style="list-style-type: none"> • MTX 7.5, 10, 15, 17.5, 20, 22.5 or 25 mg as a single dose every week • Matching placebo for MTX given as a single dose every week • Matching placebo for upadacitinib QD
Mode of Administration:	Oral
Duration of Treatment:	260 weeks (Period 1: 14 weeks; Period 2: 246 weeks)
Criteria for Evaluation:	
Efficacy:	
Period 1	
<p>The primary endpoint 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 14.</p> <p>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.</p>	

Criteria for Evaluation (Continued):

Efficacy (Continued):

Period 1 (Continued)

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

Ranked key secondary endpoints (at Week 14) 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. Change from baseline in morning stiffness (duration).

Ranked key secondary endpoints (at Week 14) 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. Change from baseline in morning stiffness (duration).

Other key secondary endpoints (at Week 14) for both US/FDA and EU/EMA regulatory purposes are:

1. ACR50 response rate;
2. ACR70 response rate;

Additional endpoints at all visits are:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in CDAI and SDAI;
- Change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in morning stiffness (severity and duration);
- Proportion of subjects achieving LDA and proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria (see below)
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22 ;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 ;
- ACR/EULAR Boolean remission;

Criteria for Evaluation (Continued):			
Efficacy (Continued):			
Period 1 (Continued):			
	DAS28 (CRP) and DAS28 (ESR)	SDAI	CDAI
LDA	≤ 3.2	≤ 11.0	≤ 10
CR	< 2.6	≤ 3.3	≤ 2.8
<p>Additional endpoints (at Weeks 4 and 14) are:</p> <ul style="list-style-type: none"> • Change from baseline in EQ-5D-5L; • Change from baseline in SF-36. <p>Period 2</p> <p>Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 20, 26, 36, 48, every 12 weeks through Week 240, and Week 260/PD:</p> <ul style="list-style-type: none"> • ACR20/50/70 response rates; • Change from baseline in individual ACR components; • Change from baseline in DAS28 (CRP); • Change from baseline in DAS28 (ESR); • Change from baseline in morning stiffness (severity and duration); • Change from baseline in CDAI and SDAI; • Proportion of subjects achieving LDA and the proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria (as defined for Period 1); • Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22; • Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3; • ACR/EULAR Boolean remission; • Proportion of subjects with no concomitant corticosteroid use among subjects with corticosteroid use at baseline). <p>Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Week 48 only:</p> <ul style="list-style-type: none"> • Change from baseline in EQ-5D-5L; • Change from baseline in SF-36. <p>Pharmacokinetic (Period 1 Only):</p> <p>Blood samples for assay of upadacitinib and possibly other concomitant medications in plasma will be collected at Weeks 2, 4, 8, and 14/Premature Discontinuation.</p> <p>Exploratory Research Variables and Validation Studies (Optional) (Period 1 Only):</p> <p>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.</p>			

Criteria for Evaluation (Continued):

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 MTX groups. The overall type I error rate of the primary and 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 MTX 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 MTX 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 and last observation carried forward 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
AST	aspartate transaminase
BCG	Bacille Calmette-Guérin
bDMARDs	biologic disease-modifying anti-rheumatic drug
BUN	blood urea nitrogen
CBC	complete blood count
CCP	cyclic citrullinated peptide
CDAI	clinical disease activity index
CGC	common gamma-chain
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
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
gp130	glycoprotein 130
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
ICH	International Conference on Harmonization
IEC	independent ethics committee
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
INR	international normalized ratio
IR	inadequate response
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus activated kinase
LDA	low disease activity
LDL-C	low-density lipoprotein cholesterol

MACE	major adverse cardiovascular event
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
MTX-IR	methotrexate inadequate responder
NA	no assessment
NMSC	non-melanoma skin cancer
NONMEM	non-linear mixed-effects modeling
NRI	non-responder imputation
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
OC	observed cases
OLE	open-label extension
PCR	polymerase chain reaction
PCS	physical component summary
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
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	Simplified 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	anti-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

2.0	Table of Contents	
1.0	Title Page	1
1.1	Protocol Amendment: Summary of Changes	3
1.2	Synopsis	9
1.3	List of Abbreviations and Definition of Terms.....	17
2.0	Table of Contents	21
3.0	Introduction	26
3.1	Differences Statement.....	29
3.2	Benefits and Risks.....	30
4.0	Study Objectives	30
5.0	Investigational Plan	31
5.1	Overall Study Design and Plan: Description	31
5.2	Selection of Study Population.....	39
5.2.1	Inclusion Criteria	39
5.2.2	Exclusion Criteria	41
5.2.3	Prior and Concomitant Therapy.....	44
5.2.3.1	Permitted Background RA Therapy.....	44
5.2.3.2	Prohibited Therapy.....	46
5.2.4	Contraception Recommendations	50
5.3	Efficacy, Pharmacokinetic, Pharmacodynamic, Exploratory Research and Validation Studies, and Safety Assessments/Variables.....	53
5.3.1	Efficacy and Safety Measurements Assessed and Flow Chart	53
5.3.1.1	Study Procedures	55
5.3.1.2	Collection and Handling of Optional Samples for Exploratory Research and Validation Studies	77
5.3.2	Drug Concentration Measurements	79
5.3.2.1	Collection of Samples for Analysis	79
5.3.2.2	Measurement Methods.....	80
5.3.3	Efficacy Variables.....	80
5.3.3.1	Period 1 Variables.....	80
5.3.3.1.1	Primary Variable.....	80

5.3.3.1.2	Key Secondary Variables.....	81
5.3.3.1.3	Additional Variables	82
5.3.3.2	Period 2 Variables.....	83
5.3.4	Safety Variables	83
5.3.5	Pharmacokinetic Variables	84
5.3.6	Exploratory Research Variables and Validation Studies	84
5.4	Removal of Subjects from Therapy or Assessment.....	84
5.4.1	Discontinuation of Individual Subjects.....	84
5.4.2	Discontinuation of Entire Study.....	87
5.5	Treatments.....	87
5.5.1	Treatments Administered.....	87
5.5.2	Identity of Investigational Product.....	89
5.5.2.1	Packaging and Labeling.....	89
5.5.2.2	Storage and Disposition of Study Drugs.....	90
5.5.3	Method of Assigning Subjects to Treatment Groups.....	90
5.5.4	Selection and Timing of Dose for Each Subject.....	91
5.5.5	Blinding.....	92
5.5.5.1	Blinding of Investigational Product	92
5.5.5.2	Blinding of Data for Data Monitoring Committee.....	93
5.5.6	Treatment Compliance.....	94
5.5.7	Drug Accountability.....	94
5.6	Discussion and Justification of Study Design.....	95
5.6.1	Discussion of Study Design and Choice of Control Groups.....	95
5.6.2	Appropriateness of Measurements.....	96
5.6.3	Suitability of Subject Population	96
5.6.4	Selection of Doses in the Study	96
6.0	Complaints	97
6.1	Medical Complaints	97
6.1.1	Definitions.....	98
6.1.1.1	Adverse Event.....	98
6.1.1.2	Serious Adverse Events	99
6.1.1.3	Adverse Events of Special Interest	100
6.1.2	Adverse Event Severity.....	100

6.1.3	Relationship to Study Drug.....	101
6.1.4	Adverse Event Collection Period.....	101
6.1.5	Serious Adverse Event Reporting.....	103
6.1.6	Pregnancy.....	105
6.1.7	Toxicity Management.....	105
6.1.8	Data Monitoring Committee.....	111
6.1.9	Cardiovascular Adjudication Committee.....	111
6.2	Product Complaint.....	111
6.2.1	Definition.....	111
6.2.2	Reporting.....	112
7.0	Protocol Deviations.....	112
8.0	Statistical Methods and Determination of Sample Size.....	113
8.1	Statistical and Analytical Plans.....	113
8.1.1	Analysis Populations.....	114
8.1.1.1	Full Analysis Set (FAS).....	114
8.1.1.2	Per Protocol Analysis Set.....	114
8.1.1.3	Safety Analysis Set.....	114
8.1.2	Subject Accountability, Disposition and Study Drug Exposure.....	114
8.1.2.1	Subject Accountability.....	114
8.1.2.2	Subject Disposition.....	115
8.1.2.3	Study Drug Exposure.....	115
8.1.3	Analysis of Demographic and Baseline Characteristics.....	115
8.1.4	Efficacy Analyses.....	116
8.1.4.1	Efficacy Analysis for Period 1.....	116
8.1.4.1.1	Primary Efficacy Variable.....	116
8.1.4.1.2	Key Secondary Efficacy Variables.....	117
8.1.4.1.3	Other Efficacy Variables.....	117
8.1.4.1.4	Multiplicity Control for Primary and Ranked Secondary Endpoints.....	118
8.1.4.1.5	Imputation Methods.....	118
8.1.4.2	Long-Term Efficacy Analysis for Period 1 and Period 2 Combined.....	119

8.1.5	Safety Analyses.....	119
8.1.5.1	General Considerations.....	119
8.1.5.2	Analysis of Adverse Events.....	120
8.1.5.2.1	Treatment-Emergent Adverse Events (TEAE).....	120
8.1.5.2.2	Serious Adverse Events and Death.....	121
8.1.5.3	Analysis of Laboratory, Vital Sign, and ECG Data.....	121
8.1.6	Pharmacokinetic and Exposure-Response Analyses.....	122
8.2	Determination of Sample Size.....	124
8.3	Randomization Methods.....	124
9.0	Ethics.....	124
9.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB).....	124
9.2	Ethical Conduct of the Study.....	125
9.3	Subject Information and Consent.....	126
10.0	Source Documents and Case Report Form Completion.....	127
10.1	Source Documents.....	127
10.2	Case Report Forms.....	128
11.0	Data Quality Assurance.....	130
12.0	Use of Information.....	131
13.0	Completion of the Study.....	132
14.0	Investigator's Agreement.....	133
15.0	Reference List.....	134

List of Tables

Table 1.	Examples of Commonly Used Strong CYP3A Inhibitors and Inducers.....	48
Table 2.	Clinical Laboratory Tests.....	71
Table 3.	Identity of Investigational Product.....	89

List of Figures

Figure 1.	Period 1 Study Design	34
Figure 2.	Period 2 Study Design	35
Figure 3.	Criteria for HBV DNA PCR Qualitative Testing	73
Figure 4.	Adverse Event Collection	102

List of Appendices

Appendix A.	Responsibilities of the Clinical Investigator	137
Appendix B.	List of Protocol Signatories.....	139
Appendix C.	Study Activities (Period 1).....	140
Appendix D.	Study Activities – Optional Samples for Exploratory Research and Validation Studies (Period 1 Only)	144
Appendix E.	Study Activities (Period 2).....	145
Appendix F.	Physician's Global Assessment of Disease Activity Example	148
Appendix G.	Joint Evaluation Worksheet Example	149
Appendix H.	Latent TB Risk Assessment Form Example	151
Appendix I.	Patient's Global Assessment of Disease Activity Example	152
Appendix J.	Patient's Assessment of Pain Example.....	153
Appendix K.	Health Assessment Questionnaire (HAQ-DI) Example.....	154
Appendix L.	Patient's Assessment of Severity and Duration of Morning Stiffness Example	157
Appendix M.	Short Form-36 (SF-36™) Health Status Survey Questionnaire Example	158
Appendix N.	EuroQoL-5D-5L Example	164
Appendix O.	Rheumatology Common Toxicity Criteria v.2.0 Example	166

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 (IC₅₀ 120 nM), which is essential for erythropoietin signaling. Upadacitinib is also less potent against JAK3 (IC₅₀ 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 ($\geq 5\%$) in the upadacitinib treated subjects were urinary tract infection, headache, upper respiratory tract infection, and nausea. There were 6 subjects (1.3% of total combined populations) with herpes zoster reactivation distributed across the upadacitinib dose groups, and 2 subjects (1.9%) in the placebo groups. In these two 12 week studies, a total of 2 subjects in the upadacitinib treatment groups reported malignancies. One subject reported non-melanoma skin cancers (NMSC) (basal cell and squamous cell carcinoma) and 1 subject was diagnosed with lung cancer 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 M15-555 differs from other upadacitinib studies as it is the first study to evaluate the safety and efficacy of upadacitinib alone versus MTX alone in the MTX-IR 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 safety and efficacy (signs and symptoms) of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone in MTX-IR subjects with moderately to severely active RA.

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 14-week, randomized, double-blind, parallel-group, controlled period designed to compare the safety and efficacy of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone for the treatment of signs and symptoms of RA in subjects with moderately to severely active RA despite stable doses of MTX (inadequate response to MTX). 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 5, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

The study is designed to enroll 600 subjects at approximately 175 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 may not be enrolled.

The study duration will include a 35-day screening period; a 14-week randomized, double-blind, parallel-group, controlled treatment period (Period 1); a 246-week blinded extension period (Period 2); and a 30-day follow-up 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: MTX (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: MTX (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Prior to enrollment subjects must have been receiving oral or parenteral MTX therapy ≥ 3 months and on a stable dose [15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week] for at least 4 weeks. No MTX washout is needed prior to randomization. Each subject will be instructed to take a required number of capsules once weekly (MTX and/or matching placebo) based on prior dose of MTX and 1 tablet once daily (upadacitinib or matching placebo) to maintain blinding (see Subject Dosing Diary and Instructions). Refer to Section 5.3.1.1, Randomization/Drug Assignment for additional information. MTX and matching placebo will be distributed as active MTX or placebo tablets over-encapsulated into identical capsules to in blister packs, to provide the correct total dose for each individual subject and to maintain blinding during Period 1. Detailed dosing instructions can be found in the Subject Dosing Diary and Instructions.

All subjects will start on their blinded upadacitinib (30 mg QD, 15 mg QD or Placebo QD) dose at Baseline. Also, starting at Baseline, all subjects will discontinue their current MTX treatment and start their blinded MTX treatment. Subjects will be given oral MTX in a blinded manner (7.5 to 25 mg/week or placebo) based on the subject's prior stable dose of MTX. Subjects who are on a stable dose of MTX between 10 and < 15 mg/week at study entry will be assigned to MTX 10 mg/week at randomization. For all other doses of MTX, subjects will be assigned to blinded MTX based on their current stable MTX dose at study entry. In addition, all subjects should take a dietary supplement of folic acid (or equivalent) throughout Period 1 participation; while in Period 2 (starting at Week 26) it should only be taken if MTX is given as background medication. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions.

Subjects who complete the Week 14 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2 (246 weeks). Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 30 mg QD or 15 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to MTX treatment group in Period 1 will discontinue MTX and

receive upadacitinib 30 mg QD or 15 mg QD in a blinded fashion per their pre-specified randomization assignments.

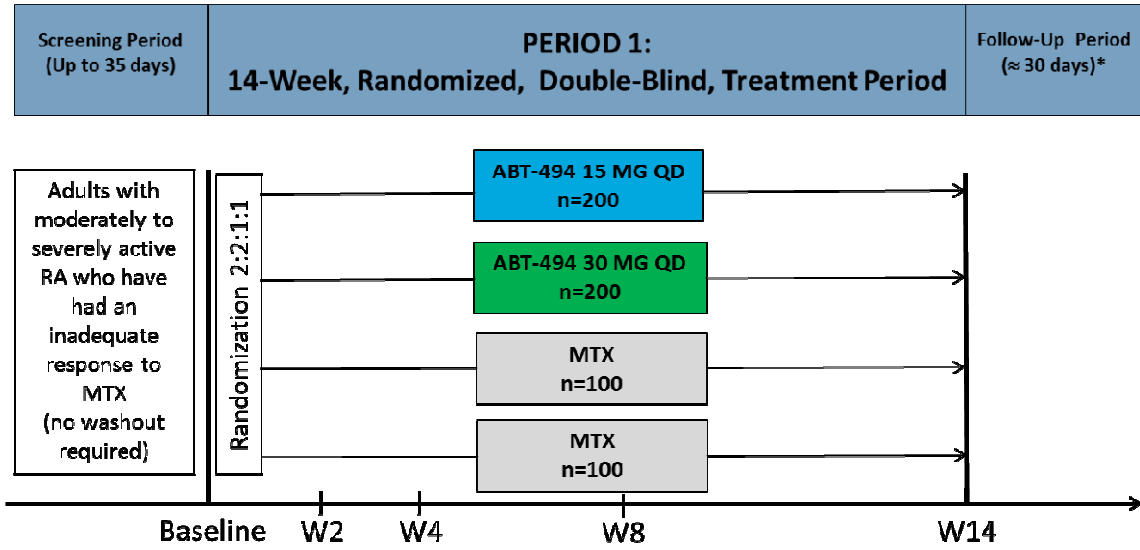
In Period 2, subjects who do not achieve LDA as defined by CDAI \leq 10 at Week 26 should have background medication(s) adjusted or initiated as rescue (refer to Section 5.2.3.1 for Permitted Background RA Therapy) after assessments for Week 26 have been completed.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 14). Study sites and subjects will remain blinded for the duration of the study (Period 1 and Period 2).

Starting with Amendment 5, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

Study design schematics of Period 1 and Period 2 are shown in [Figure 1](#) and [Figure 2](#), respectively.

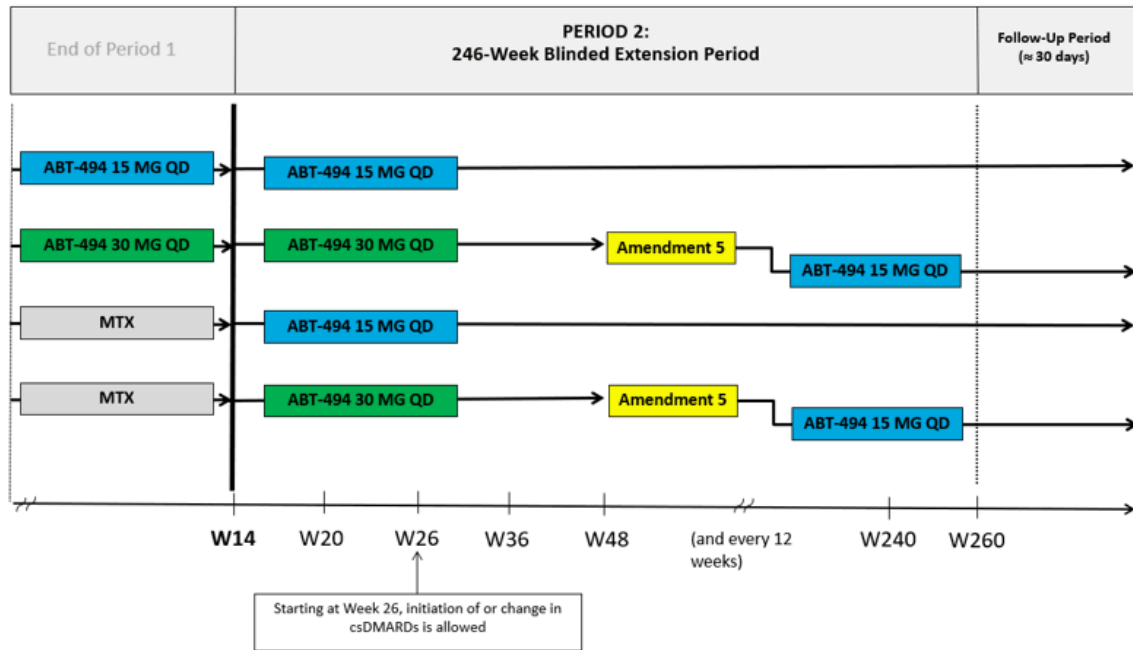
Figure 1. Period 1 Study Design



MTX = methotrexate; n = number; QD = once daily; RA = rheumatoid arthritis; W = week

* 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; MTX = methotrexate; QD = once daily; RA = rheumatoid arthritis; W = week

Note: Starting with Amendment 5, 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 [Appendix C](#). Lab values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure with no additional re-screening possible. Redrawing samples if initial samples were unable to be analyzed would not count as a retest since initial result was never obtained.

Subjects that initially screen fail for the study are permitted to re-screen once following re-consent. Lab values can be re-tested once during the re-screening period. For

additional re-screenings, 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) or a purified protein derivative (PPD) test (or equivalent), 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 and no more than 90 days have passed.

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

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

Period 2 (Long-Term Extension Period [246 Weeks])

Period 2 will begin at the Week 14 Visit after all assessments have been completed. During Period 2, subjects will have a study visit at Weeks 20, 26, 36, 48, every 12 weeks through Week 240 and Week 260/PD. A ± 7 day window is permitted around scheduled study visits. Starting at Week 26 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 26) (see Section 5.4.1) must be discontinued from study drug.

Starting with Amendment 5, 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 visit (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 Activity Schedule (Appendix E), 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 26 and visits thereafter, as well as the CDAI calculation at Week 26, if applicable. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

Premature Discontinuation of Study (Withdrawal of Informed Consent) (Period 1 and Period 2)

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time (refer to Section 5.4.1 for additional details). If a subject prematurely discontinues study drug treatment AND study participation (withdrawal of 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 visit (or phone call, if a visit is not possible) may

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

Follow-Up Visit

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

- Completed the last visit of Period 1 (Week 14), but decided not to participate in the extension Period 2; OR
- Completed the last visit of Period 2; OR
- Prematurely discontinued study drug and 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. Vital signs and laboratory test may not be required. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least one study visit at least approximately 30 days after last dose.

Protocol Modification 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 175 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 must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose [15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week] for ≥ 4 weeks prior to first dose of study drug.
4. Must have discontinued all csDMARDs other than MTX (see Inclusion Criterion 3) ≥ 4 weeks prior to first dose of study drug. The washout period for specific csDMARDs prior to first dose of study drug is specified below or should be at least five times the mean terminal elimination half-life of a drug:
 - ≥ 4 weeks for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
 - ≥ 8 weeks for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).
5. 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.

-
6. Stable dose of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids for stable medical conditions are allowed but must have been at a stable dose ≥ 1 week prior to the first dose of study drug.
 7. Subjects must have discontinued all high-potency opiates for at least 1 week and traditional Chinese medicine for at least 4 weeks prior to the first dose of study drug (refer to Section 5.2.3.2 for prohibited medications).
 8. Women of childbearing potential (refer to Section 5.2.4), must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing.

Note: Subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
 9. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 180 days after the last dose of study drug.
 10. Male subjects who are sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 180 days after the last dose of study drug to practice the protocol-specified contraception (refer to Section 5.2.4).
 11. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

- | | |
|--------|--|
| 1 – 7 | To select the appropriate subject population |
| 8 – 10 | Upadacitinib is teratogenic in both rats and rabbits. The effect of upadacitinib on human pregnancy and reproduction is unknown. |
| 11 | 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. Prior exposure to any bDMARDs.
3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms]). Current diagnosis 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 5 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 180 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 180 days after the last dose of study drug.

-
8. Any active, chronic or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or known history of human immunodeficiency virus (HIV). HBV, HCV and HIV infections are defined as:
 - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for Hepatitis B core antibody (HBc Ab) positive (+) subjects;
 - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
 - HIV: confirmed positive anti-HIV antibody (HIV Ab) test.
 9. Subject has active TB or meets TB exclusionary parameters (refer to Section 5.3.1.1 for specific requirements for TB testing).
 10. Systemic use of known strong cytochrome P450 3A (CYP3A) 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 (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for GI perforation per investigator judgment.
-

15. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome.
16. 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. Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug.
19. History of an allergic reaction or significant sensitivity to constituents of the study drug(s) (and their excipients) and/or other products in the same class.
20. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:
 - Serum aspartate transaminase (AST) $> 2 \times$ ULN;
 - Serum alanine transaminase (ALT) $> 2 \times$ ULN;
 - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m²;
 - Total white blood cell (WBC) count $< 2,500/\mu\text{L}$;
 - Absolute neutrophil count (ANC) $< 1,500/\mu\text{L}$;
 - Platelet count $< 100,000/\mu\text{L}$;
 - Absolute lymphocyte count $< 800/\mu\text{L}$;
 - Hemoglobin < 10 g/dL.
21. History of any of the following cardiovascular conditions:
 - Moderate to severe congestive heart failure (New York Heart Association class III or IV);
 - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
 - Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;

- Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.
22. Clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 500 msec.

Rationale for Exclusion Criteria

- | | |
|---------------|---|
| 1 – 3 | To select the appropriate subject population |
| 6 – 7 | Upadacitinib is teratogenic in both rats and rabbits. The impact of upadacitinib on human pregnancies is unknown. |
| 4 – 5, 8 – 22 | To ensure safety of the subjects throughout the study |

5.2.3 Prior and Concomitant 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

All subjects should take a dietary supplement of folic acid (or equivalent, such as folinic acid) throughout Period 1 participation; while in Period 2 (starting at Week 26) it should only be taken if MTX is given as background medication. Folic acid dosing and timing of

regimen should be followed according to Investigator's instructions. AbbVie will not provide the folic acid (or equivalent).

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 study entry, these must not be initiated during the first 26 weeks of study. Initiation of or changes in doses are allowed starting at Week 26 (after Week 26 assessments have been performed)
- If taking any of the above including low potency analgesics, i.e., tramadol, codeine, hydrocodone, or propoxyphene at study entry 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. For NSAIDs, acetaminophen/paracetamol, tramadol, codeine, hydrocodone, and propoxyphene, or oral steroids, changes in dose, including initiation, are not allowed until Week 26.

In Period 2, subjects who do not achieve LDA as defined by CDAI ≤ 10 at Week 26 should have background medication(s) adjusted or initiated (see below) after assessments for Week 26 have been finished. Initiation of or change in corticosteroids, NSAIDs, acetaminophen, or initiation of up to 2 csDMARDs (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide except the combination of MTX and leflunomide) is allowed as per local label.

Starting at Week 26 (after Week 26 assessments have been performed) 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. To avoid confounding effects of systemic absorption of intra-articular corticosteroids, joint injections should be avoided, if possible, within 21 days prior to the next scheduled study visit. 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.

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

Local label requirements for MTX should be followed, including complying with contraindicated concomitant therapies (i.e., trimethoprim-sulfamethoxazole).

JAK Inhibitor

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

Corticosteroids

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

Biologic Therapies

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

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

Therapies including but not limited to the following biologic therapies are prohibited medications through the end of study drug administration:

- 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)

csDMARD Therapies

Subjects must have discontinued all csDMARDs (other than MTX) prior to the first dose of study drug as specified in the washout procedures (Inclusion Criterion 6, Section 5.2.1).

Starting at Week 26 (after Week 26 assessments have been performed) and thereafter, initiation of csDMARDs (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and to concomitant use of up to

2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label.

Strong CYP3A Inhibitors or Inducers

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

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

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir Clarithromycin Cobicistat Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Avasimibe Carbamazepine Phenytoin Rifapentine Rifampin 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 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in this study. Investigational drugs are also prohibited during the study.

Vaccines

Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) 4 weeks before first dose of study drug with appropriate precautions. Live vaccinations are prohibited 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.

Traditional Chinese Medicine

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

5.2.4 Contraception Recommendations

Contraception Recommendation for Females

A woman who is postmenopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) is not considered to be a woman

of childbearing potential and is not required to follow contraception recommendations.

Postmenopausal is defined as:

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

If the female subject is $<$ 55 years of age:

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

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

For a female subject at any age:

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

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

- 180 days after last dose of study drug if subject completed **last dose of study drug in Period 1**
- 30 days after last dose of study drug if subject completed **last dose of study drug in Period 2**
- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Baseline.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Baseline.
- 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 (if acceptable per local requirements): 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).

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

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during and after exposure to the investigational therapies, upadacitinib, and MTX.

Contraception recommendations related to use of concomitant therapies prescribed per standard of care (including concomitant csDMARDs) should be based on the local label.

Contraception Recommendation for Males

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

Contraception requirements related to the 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 [Appendix C](#), [Appendix D](#), and [Appendix E](#).

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 the subject's home residence (see Section 5.3.1.1 – Sub-Section "Home Healthcare Visits")
- 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 do not need to be performed:
 - Patient questionnaires
 - Vital signs and body weight
 - Physical exam
 - Physician Global Assessment (PhGA)
 - TJC68/SJC66
- The following activities may be performed by a local clinic/hospital/laboratory. All procedures performed at local facilities must be performed by qualified personnel:
 - 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
- Laboratory tests (blood chemistry, hematology, urinalysis)
- ESR

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

- Laboratory 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.

5.3.1.1 Study Procedures

The study procedures outlined in [Appendix C](#) and [Appendix E](#) are discussed in detail in this section, with the exception of exploratory research and validation studies (discussed in Section [5.3.1.2](#)), drug concentration measurements (discussed in Section [5.3.2](#)), the collection of prior and concomitant medication information (discussed in Section [5.2.3](#)), and the collection of AE information (discussed in Section [6.0](#)). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

At the Screening visit, the subject will sign and date a study specific, IEC/IRB approved, informed consent 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. The separate written consent may be part of the main consent form. 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 [Appendix C](#) and [Appendix E](#); 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 I](#))
- Patient's Assessment of Pain VAS ([Appendix J](#))
- Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess the physical function and health-related quality of life of each subject ([Appendix K](#))
- Patient's Assessment of Severity and Duration of Morning Stiffness Numerical Rating Scale (NRS) ([Appendix L](#))*
- EuroQoL-5D-5L (EQ-5D-5L) ([Appendix N](#))
- Short Form-36 (SF-36) ([Appendix M](#))

Period 2

- Patient's Global Assessment of Disease Activity VAS ([Appendix I](#))
- Patient's Assessment of Pain VAS ([Appendix J](#))
- HAQ-DI to assess the physical function and health-related quality of life of each subject ([Appendix K](#))
- Patient's Assessment of Severity and Duration of Morning Stiffness NRS ([Appendix L](#))*
- EQ-5D-5L ([Appendix N](#)) (Week 48 only)
- SF-36 ([Appendix M](#))

* 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

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

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form ([Appendix H](#)) 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.

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 (TA MD). The results of the TB test(s) will be retained at the site as the original source documentation.

For subjects with a negative TB test result at Screening or most recent evaluation, an annual TB re-test will be performed. The TB test(s) to be performed depends on local guidelines and whether or not the site has capacity to perform Quantiferon TB Gold

testing (see below). If an annual TB test is newly positive (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Any positive TB screen after the patient has started the study should be reported as an AE of latent TB or active TB (as applicable).

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.

TB test:

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD are not required to repeat either test at Screening or during the study and should be considered positive.
- For regions that require both PPD and Quantiferon TB Gold testing, both will be performed. A positive TB test is defined by local guidelines (for example, in some countries, both PPD and Quantiferon TB Gold tests are performed, and if either one is positive, the TB test is considered positive).
- In the absence of local guidelines defining a positive result when both PPD and Quantiferon TB Gold are performed, then the Quantiferon TB Gold test result will be the TB test result (QF supersedes PPD).
- 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 test 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 method.
- 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 the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the patient is considered to be negative.

- 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.

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

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with no signs or symptoms and a CXR not suggestive of active TB may be enrolled after initiation of TB prophylaxis (see below). Subjects with evidence of active TB must not be enrolled.

TB prophylaxis:

At Screening, if the subject has evidence of latent TB infection (positive TB test 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.

Obtain a CXR every 48 weeks for subjects with newly identified TB risk factors as determined by the TB risk assessment form ([Appendix H](#)) or for subjects living in areas endemic for TB or for subjects with newly positive PPD or QuantiFERON-TB Gold test.

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.

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

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 H](#)), 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 Medical Monitor before enrolling the subject.

12-Lead ECG

For all subjects, a resting 12-lead ECG will be performed at screening, Week 48 and every 48 weeks thereafter, as specified in [Appendix C](#) and [Appendix E](#). For subjects who do not enter Period 2 or prematurely discontinue from study, an ECG will be performed at their final visit as indicated in [Appendix C](#) and [Appendix E](#). A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. ECG with QT interval corrected for heart rate using Fridericia'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 these cases, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible site monitor and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available and provided nothing has changed in the subject's medical history to warrant a repeat test. If there are other findings that are clinically significant, the Investigator must contact the AbbVie Therapeutic Area Medical Director before enrolling the subject.

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

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 as specified in [Appendix C](#) and [Appendix E](#). 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 [Appendix C](#) and [Appendix E](#). 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 [Appendix C](#) and [Appendix E](#). The physical examination at the Baseline Visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted by the Investigator at Baseline prior to the first dose of study drug will be recorded in the subject's medical history; abnormalities noted after the first dose of study drug will be evaluated and documented by the Investigator as to whether or not the abnormality is an AE (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 [Appendix C](#) and [Appendix E](#), 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 F](#)).

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

SJC Assessment

An assessment of 66 joints ([Appendix G](#)) will be done by directed physical examination at visits specified in [Appendix C](#) and [Appendix E](#). The joints to be examined for swelling are the same as those examined for tenderness, except the hip joints are excluded. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9") or no assessment ("NA").

Any injected 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 study as much as possible. A back-up independent joint assessor should be identified. The independent joint assessor 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 and will be performed at the Week 26 visit. An Interactive Response Technology (IRT) will calculate CDAI with input from site personnel on joint counts and the subject's and physician's Global Assessment of RA Disease Activity score.

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

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

NOTE: Investigator should optimize background RA therapies (as rescue) in subjects who failed to achieve a $\text{CDAI} \leq 10$.

Pregnancy Test

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

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the study;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study.

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

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

borderline, a repeat test is required (≥ 3 days later) to document continued lack of a positive results.

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, return to the study site and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory.

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

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 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.

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 in this study or be allowed to continue study drug.

Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests listed in Table 2. Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per Investigator's discretion. A certified central laboratory will be utilized to process and

provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

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

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 [Appendix C](#) and [Appendix E](#). Blood draws should be performed only after all questionnaires (HAQ-DI, Patient's Assessment of Pain, etc.), clinical assessments, and vital sign determinations are obtained.

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

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

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

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

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

Table 2. Clinical Laboratory Tests

Hematology (Central Lab)	Clinical Chemistry ^a (Central Lab)	Urinalysis ^b (Central Lab)	Other Laboratory Tests
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils 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 Rheumatoid Factor ^e Anti-CCP autoantibodies ^e hs-CRP ^f IgG and IgM FSH ^g HIV Ab ^{e,h} <u>Local Lab Tests:</u> Urine pregnancy test ⁱ ESR

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; FSH = follicle stimulating hormone; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; 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

- Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.
- INR will only be measured with a separate blood sample at repeat testing if ALT and/or AST > 3 × ULN.
- A serum pregnancy test will be performed for all women of childbearing potential at the Screening Visit and if postbaseline urine pregnancy test turns positive.

Table 2. Clinical Laboratory Tests (Continued)

- e. HBV DNA testing is required for subjects who meet specific toxicity management criteria (See ALT/AST toxicity management criteria in [Table 4](#)).
- f. 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 the 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 5, 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.
- g. At screening for women < 55 years old and has had no menses for ≥ 12 months and has no history of permanent surgical sterilization.
- h. Anti-HIV Ab will be performed at Screening, unless prohibited by local regulations. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.
- 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. 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 permanently discontinued. In the event a pregnancy test comes back borderline, a repeat test is required. If a urine pregnancy test at post-baseline is positive, study drug needs to be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If serum pregnancy test is negative, study drug may be restarted. If the serum pregnancy test is positive, study drug must be permanently discontinued.

Hepatitis Screen

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

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)

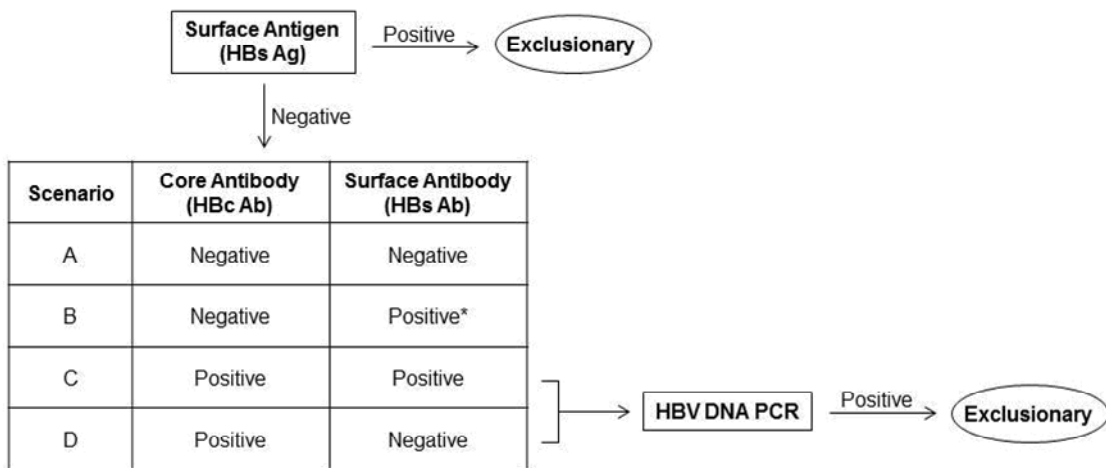
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

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 HIV infection are excluded from study participation. HIV testing will be performed at Screening, unless prohibited by local regulations. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

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

Randomization will be stratified by geographic region at Screening.

Randomization should occur within 2 days of the day of the week that the subject would normally take their MTX dose. For example, if a subject took MTX last Monday, then randomization should take place between the following Monday to Wednesday.

See Section 5.5.3 for details.

Study Drug Dispensing, Dosing, and Compliance

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

To maintain the blind in this study with two blinded investigational study drugs (MTX and upadacitinib), each subject will be instructed to take a required number of capsules once weekly (MTX and/or matching placebo) based on prior dose of MTX and 1 tablet once daily (upadacitinib or matching placebo). MTX and matching placebo will be distributed as identical capsules to maintain blinding. Upadacitinib and matching placebo will be distributed as identical tablets to maintain blinding.

Determination of which subjects are assigned to receive MTX-placebo versus upadacitinib placebo will be via the IRT (Interactive Response Technology), which will randomly assign each subject to the appropriate treatment group in a blinded manner.

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
- Study drug can be administered by the subject (or subject's caregiver) at home
- 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 sample 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 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 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 the completion of Period 1.

DNA Samples for Pharmacogenetic or Epigenetic Analyses

Whole blood samples for DNA isolation will be collected at the visits indicated in [Appendix D](#) 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 [Appendix D](#) 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 [Appendix D](#) 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 2 and 4 prior to dosing;
- Weeks 8 and 14/PD at any time during the visit.

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

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

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

5.3.2.2 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Period 1 Variables

5.3.3.1.1 Primary Variable

The primary endpoint 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 14. Analyses will be conducted separately for US/FDA regulatory purposes and EU/EMA regulatory purposes; for each set of analysis, only one primary endpoint is specified.

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

LDA is defined as $DAS28 (CRP) \leq 3.2$. 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 14.

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

* 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 $\sqrt{}$ is square root and \ln is natural log.

5.3.3.1.2 Key Secondary Variables

Ranked key secondary endpoints (at Week 14) 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 Clinical remission (CR) based on DAS28 (CRP);
6. Change from baseline in morning stiffness (duration).

Ranked key secondary endpoints (at Week 14) 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. Change from baseline in morning stiffness (duration).

Other key secondary endpoints (at Week 14) for both US/FDA and EU/EMA regulatory purposes are:

1. ACR50 response rate;
2. ACR70 response rate;

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 CDAI and SDAI;
- Change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in morning stiffness (severity and duration);
- 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)
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22 ;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 ;
- ACR/EULAR Boolean remission;

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

Additional endpoints (at Weeks 4 and 14) are:

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

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 20, 26, 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 morning stiffness (severity and duration);
- Change from baseline in CDAI and SDAI;
- 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 (as defined for Period 1);
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.22 ;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 ;
- ACR/EULAR Boolean remission;
- Proportion of subjects with no concomitant corticosteroid use (among subjects with corticosteroid use at baseline).

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

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

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

5.3.6 Exploratory Research Variables and Validation Studies

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to nucleic acids, proteins, lipids or metabolites.

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of RA or related conditions and/or upadacitinib or drugs of similar classes. These 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 have study drug discontinued immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and 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 study 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 study as determined by the Investigator or the AbbVie Therapeutic Area Medical Director.
- Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injury).
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.
- Starting at Week 26, 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 26) 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 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, 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. For subjects who prematurely discontinue study drug AND study participation (withdrawal of informed consent), if subject is willing, a 30-day follow-up visit 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.

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. Vital signs and laboratory test may not be required. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least one study visit at least approximately 30 days after last dose.

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

There are two active study drugs in this study (Period-1). The first is daily upadacitinib (30 mg QD or 15 mg QD) and the second is weekly MTX. In Period 2, all subjects will be assigned to daily upadacitinib (30 mg QD or 15 mg QD).

Upadacitinib (or matching placebo) study drug will be taken orally once daily, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day. The

study drug can be taken with or without food. The last dose of upadacitinib/placebo tablets in Period 1 is taken the day prior to the Week 14 visit.

MTX (or matching placebo) study drug will be taken orally once weekly, beginning on Day 1 (Baseline), and should be taken the same day and approximately the same time each week. The study drug can be taken with or without food. The last dose of MTX/placebo capsules in Period 1 is taken at Week 13 prior to the Week 14 visit.

Each subject will be instructed to take a required number of capsules once weekly (MTX and/or matching placebo) based on prior MTX dose and 1 tablet once daily (Upadacitinib or matching placebo) to maintain blinding. Detailed dosing instructions can be found in the Subject Dosing Diary and Instructions.

Subjects should be instructed not to take the upadacitinib/placebo or the MTX/placebo study drug on the day of the Week 14 visit. At the Week 14 visit, after all Period 1 assessments have been completed, subjects will begin long term extension Period 2 and receive Period 2 blinded upadacitinib (30 mg or 15 mg) tablets once daily. Starting with Amendment 5, all subjects will receive open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD.

Subjects should take a dietary supplement of folic acid beginning on Day 1 (Baseline) throughout Period 1 participation; while in Period 2 (starting at Week 26) it should only be taken if MTX is given as background medication. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions.

When the last subject completes the Week 14 visit of Period 1, the study conduct of Period 1 will be unblinded only to the Sponsor for the purpose of regulatory submission. Study sites and subjects will remain blinded throughout Periods 1 and 2.

If a subject is unable to come to the study site to pick up their study drug due to state of emergency or any pandemic like COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations.

AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to Section 5.3.1.1 for details on DTP shipment of study drug.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 3.

Table 3. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib (ABT-494)	oral	tablet	15 mg 30 mg	AbbVie
Upadacitinib (ABT-494) matching placebo	oral	tablet	NA	AbbVie
MTX	oral	2.5 mg tablet over-encapsulated in hard gelatin capsule	7.5 mg 10 mg	Over-encapsulated MTX capsule: Fisher Clinical Services for AbbVie MTX tablet: Dava Pharmaceuticals Orion and/or Hexal AG and/or Goldshield
MTX matching placebo	oral	capsule	NA	Fisher Clinical Services and/or AbbVie

Folic acid will be supplied by the subject, according to Investigator's instructions for dosing and timing of administration.

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. Methotrexate and matching placebo will be packaged in blister packs 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

Study drugs 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 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) 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: MTX (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: MTX (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Randomization will be stratified by 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 5, 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 2 and Week 4 visits).

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

Upadacitinib/Placebo tablets (daily dosing):

- If a subject should forget to take their daily upadacitinib (or matching placebo) dose at their regularly scheduled dosing time, he/she 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 upadacitinib/placebo interruption
 - > 7 consecutive days during Weeks 1 through 14 (Period 1) or
 - > 30 consecutive days after Week 14 (Period 2), they should notify their

Investigator, and the Investigator will determine if study drug should be restarted. If study drug treatment is interrupted or withdrawn in Period 1, both daily and weekly study drug administration must be stopped.

MTX/Placebo capsules (weekly dosing):

- Weekly MTX (or matching placebo) should be taken the same day and approximately the same time each week. If the subject should forget to take their oral MTX (or matching placebo) dose on their regularly scheduled dosing date, he/she should take the forgotten dose as soon as they remember. If more than 72 hours has elapsed since the missed dose, the subject should contact their Investigator for further dosing instructions. The study drug can be taken with or without food.
- If the subject experiences a study drug interruption ≥ 2 consecutive missed doses in Period 1 (other than for reasons listed in Section 6.1.7), he/she should notify their Investigator, and study drug should be discontinued. If study drug treatment is interrupted or withdrawn in Period 1, both daily and weekly study drug administration must be stopped.

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 study (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 5, 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 and placebo tablets along with MTX and placebo capsules 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 emergency 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 request 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 14) for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study.

Starting with Amendment 5, 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 multicenter study includes two periods.

Period 1 is a 14-week, randomized, double-blind, parallel-group, controlled treatment period to compare safety and efficacy of upadacitinib 30 mg QD alone and 15 mg QD alone versus continuing MTX alone in subjects with moderately to severely active RA who are on a stable dose of MTX and have an inadequate response to MTX. Period 1 is designed to test superiority of upadacitinib versus MTX for achieving the primary endpoint (ACR20 for US/FDA regulatory purposes or LDA for EU/EMA regulatory purposes) at Week 14.

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 30 mg QD or 15 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to MTX in Period 1 will be switched to receive upadacitinib 30 mg or 15 mg QD in a blinded fashion per their pre-specified randomization assignments. Dose reduction or escalation of upadacitinib during Period 2 is not permitted to allow unbiased assessments of long-term safety and efficacy of upadacitinib 30 mg QD versus 15 mg QD.

Starting with Amendment 5, 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 MTX treatment. This study will 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 who have had an inadequate response to MTX treatment, but are able to tolerate ≥ 15 mg of weekly oral MTX or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week. Local guidelines for MTX dosage may apply. 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 level ≥ 3 mg/L (central lab) at Screening.

5.6.4 Selection of Doses in the Study

Two doses of the once-daily formulation of upadacitinib will be evaluated: upadacitinib 30 mg QD and 15 mg QD. The dose selection in this study is based on extrapolation of

pre-clinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the Phase 1 studies in healthy volunteers (single and multiple ascending dose Studies M13-401 and M13-845, respectively) and Phase 2 studies in RA subjects (Studies M13-537 and M13-550). The doses selected for Study M15-555, upadacitinib 30 mg QD and 15 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 drug, 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 adverse event meets any of the following criteria, it is to be reported to AbbVie as a SAE within 24 hours of the site being made aware of the SAE.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

6.1.1.3 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;
- Elevated creatine phosphokinase (CPK);
- Adjudicated embolic and thrombotic events (non-cardiac, non-CNS).

6.1.2 Adverse Event Severity

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

6.1.3 Relationship to Study Drug

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

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

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

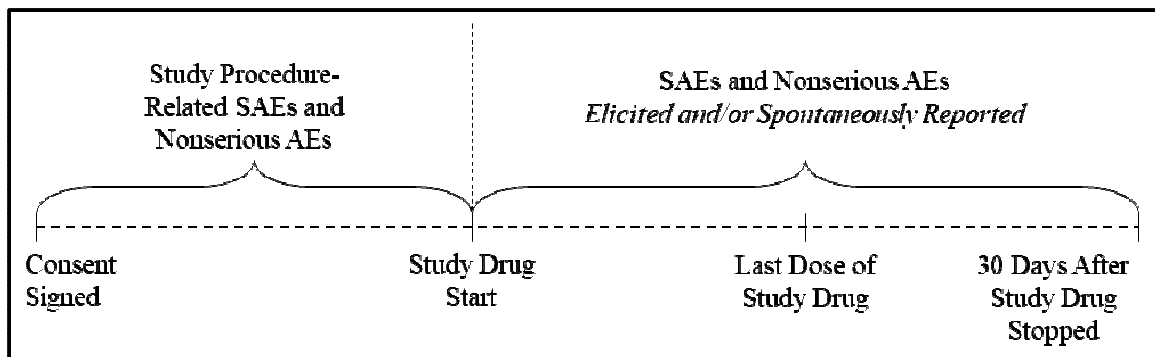
If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

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. 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 their remainder of the 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 case 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
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FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:


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

Toll Free: +1 (833) 942-2226

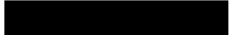
Email: GPRD_SafetyManagement_Immunology@abbvie.com

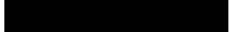
For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:


Medical Director
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: 

Mobile: 

Fax: 

Email: 

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

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

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 180 days (Period 1) or 30 days (Period 2) after the last study drug administration. 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 have had study drug discontinued and are instead on standard of care therapies, these toxicity management requirements do not apply (including alerts from the

central lab) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Re-challenge with study drug may occur once the infection has been successfully treated. 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 4](#) 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 4](#), the repeat testing must occur as soon as possible.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	<ul style="list-style-type: none"> • If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	<ul style="list-style-type: none"> • If confirmed < 1000 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)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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%). • If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample and contact the TA MD. • Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. <p>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.</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ ALT > 5 × ULN <u>OR</u> ○ 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 1 week for recommendation regarding subsequent treatment <p>For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.</p>
Serum Creatinine	<ul style="list-style-type: none"> • 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. <p>For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.</p>

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

Laboratory Parameter	Toxicity Management Guideline
Creatine Phosphokinase	<ul style="list-style-type: none"> • If confirmed CPK value $\geq 4 \times$ ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK $\geq 4 \times$ ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and inform AbbVie Therapeutic Area Medical Director. <p>For the above CPK elevation scenarios, complete supplemental CPK eCRF.</p>

For allowed study drug interruption, the following rules apply:

Period 1

- Upadacitinib/Placebo tablet (daily dosing):
 - Allow study drug interruption up to 7 consecutive days for AEs and emergency surgery.
- MTX/Placebo capsules (weekly dosing):
 - Allow study drug interruption up to 2 consecutive missed doses for AEs and emergency surgery.
- 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.
- Elective surgery will not be allowed during this 14-week-period.

Period 2

- Upadacitinib tablet (daily dosing):
 - 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.
 - 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 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.

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 AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

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

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

Office: [REDACTED]

Email: [REDACTED]

Alternate Contact:

[REDACTED]
Study Management Associate III
AbbVie Inc.

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

Office: [REDACTED]

Fax: [REDACTED]

Email: [REDACTED]

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

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 14). 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 at the end of Period 1. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

Starting with Amendment 5, 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.

Study drug compliance will be summarized for each treatment group for Period 1. The compliance is defined as the number of tablets/capsules taken (i.e., the difference between the number of tablets/capsules dispensed and the number of tablets/capsules returned) during the subject's participation in Period 1 divided by the number of tablets/capsules a subject is supposed to take each day/week 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 Analyses

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 MTX groups (Groups 3 and 4) will be combined and treated as one MTX group for analysis purposes. Each upadacitinib dose will be compared with the combined MTX group.

8.1.4.1.1 Primary Efficacy Variable

The primary endpoint (at Week 14) for US/FDA regulatory purposes is listed in Section 5.3.3.1.1. The primary endpoint (at Week 14) for EU/EMA regulatory purposes is also listed in Section 5.3.3.1.1. Analyses will be conducted separately for US/FDA regulatory purposes and EU/EMA regulatory purposes; for each set of analysis, only one primary endpoint is specified.

The analysis of the primary efficacy endpoints will be conducted on the FAS based on the treatment as randomized. The comparisons of the two primary endpoints will be made between the upadacitinib group and the combined MTX group using the Cochran-Mantel-Haenszel test adjusting for main stratification factors. For the primary analysis, Non-Responder Imputation (NRI) will be used. In addition, sensitivity analysis will be done using Observed Cases (OC). Supportive analysis will also be conducted on the Per Protocol Analysis Set.

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

8.1.4.1.2 Key Secondary Efficacy Variables

Key secondary endpoints (at Week 14) for US/FDA regulatory purposes are listed in Section 5.3.3.1.2. Key secondary endpoints (at Week 14) 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 endpoints will be conducted.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Between-group comparisons for the upadacitinib treatment group and the combined MTX treatment group will be performed using the analysis of covariance model with treatment 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, including visits beyond Week 14. 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 Primary and Ranked Secondary Endpoints

The overall type I error rate of the primary and ranked key secondary endpoints for the two doses of upadacitinib 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 impute missing data multiple times under appropriate random variation and thus generate multiple imputed "pseudo-complete" datasets. Results will be aggregated across the multiple imputed datasets, overcoming drawbacks of the single imputation methods.

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

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 the 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 continue 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 AE;
- 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 SOC's 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 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 or 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.

8.2 Determination of Sample Size

The planned total sample size of 600 for this study provides at least 90% power to detect a 21% difference in ACR20 response rate (assuming an ACR20 response rate of 37% in the MTX group), as well as at least 90% power to detect a 22% difference in LDA response rate based on DAS28 (CRP) criteria (assuming an LDA response rate of 15% in the MTX group), at two-sided $\alpha = 0.025$ and accounting for 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), ACR50, change from baseline in HAQ-DI, CR based on DAS28 (CRP), and change from baseline in 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: MTX (N = 100) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: MTX (N = 100) (Period 1) → Upadacitinib 15 mg QD (Period 2)

Randomization will be stratified by geographic region at Screening.

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

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

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

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

Due to pandemic situations 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 form, 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 study 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
 - 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 Severity and Duration 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 study. This access will be available for the duration of the study to the site investigator, as

well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected by the following 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. Another alternative of site training may include module training via a study portal.

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.

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 [Appendix C](#) and [Appendix E](#)). The data from these analyses will be electronically transferred from the central laboratory to the study database.

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

12.0 Use of Information

Any research that may be done using optional exploratory research/validation samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research/validation studies may be provided to investigators and used in scientific publications or presented at medical conventions. Exploratory research/validation 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 (EMA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

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

Protocol Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX

Protocol Date: 04 December 2020

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the 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]	Medical Director	Therapeutic Area
[REDACTED]	Senior Scientific Director	Therapeutic Area
[REDACTED]	Senior Medical Director	Pharmacovigilance and Patient Safety
[REDACTED]	Senior Director and Statistics Therapeutic Area Head	Statistics
[REDACTED]	Director	Statistics
[REDACTED]	Assistant Director	Clinical Pharmacokinetics and Pharmacometrics
[REDACTED]	Study Project Manager II	Clinical Program Development

Appendix C. Study Activities (Period 1)

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 14/PD ^a	30-Day F/U Visit ^c
	D -35 to D -1	D1 ^b	D15	D29	D57	D99	
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
Prior/concomitant therapy	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	
Patient questionnaires ^g SF-36 EQ-5D-5L		X		X		X	
Latent TB risk assessment form ^h	X						
Central lab QuantiFERON-TB Gold test ^h (and/or local TB test)	X						
Chest x-ray	X ⁱ						
12-lead ECG	X ^j					X ^k	

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 14/PD ^a	30-Day F/U Visit ^c
	D -35 to D -1	D1 ^b	D15	D29	D57	D99	
Height (screening only) and weight	X	X	X	X	X	X	X
Vital signs ^l	X	X	X	X	X	X	X
Physical exam ^m	X	X				X	
Physician Global Assessment (PhGA)		X	X	X	X	X	
TJC68/SJC66	X	X	X	X	X	X	
Serum pregnancy test at central lab ⁿ	X						
Local urine pregnancy test ^o		X	X	X	X	X	X
Central Lab Tests hsCRP ^p Blood chemistry ^q Hematology (CBC) Urinalysis ^r FSH ^s	X	X	X	X	X	X	X
ESR (local lab)	X	X	X	X	X	X	
Other Central Lab Tests Rheumatoid factor Anti-CCP autoantibodies HBV/HCV/HIVAB ^t screening	X						
IgG and IgM (central lab)		X				X	
Blood samples for upadacitinib PK assay			X ^u	X ^u	X ^v	X ^v	
Blood samples for exploratory research and validation studies (optional – see Appendix D) ^w		X	X	X		X	
Randomization/drug assignment		X					

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 14/PD ^a	30-Day F/U Visit ^c
	D -35 to D -1	D1 ^b	D15	D29	D57	D99	
Dispense study drug and subject dosing diary		X		X	X	X ^s	
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; 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 Assessment of Disease Activity; PK = pharmacokinetics; PPD = purified protein derivative; PtGA = Patient's Global Assessment of Disease Activity; SAE = serious adverse event; SD = Study Drug Discontinuation; SF-36 = 36-Item Short Form Health Survey; SJC = Swollen Joint Count; TB = tuberculosis; TJC = Tender Joint Count; VAS = visual analog scale; Wk = Week

- a. If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks 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. Document 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. For subjects who do not enter Period 2 or prematurely discontinue from the study, an ECG will be performed.
- l. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

- m. A full physical exam is required at the visits indicated. A symptom-directed physical exam may be performed when necessary.
- n. For all women of childbearing potential, 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.
- o. For all women of childbearing potential, collect urine for pregnancy test at Baseline and all subsequent visits. If urine pregnancy test is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from study drug. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.
- p. 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. For safety evaluations of signs and symptoms of infection and management of adverse events, the investigator may locally test procalcitonin. Results of tests such as hsCRP may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. Any local hsCRP or CRP tests should not be reported to the investigator until treatment allocation is unblinded or subject is known to be receiving upadacitinib. In Period 2, the central lab hsCRP results will remain blinded to Investigator, study site personnel, and the subject.
- q. 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.
- r. 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.
- s. FSH should be tested at Screening 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 in Section 5.2.4).
- t. Anti-HIV Ab will be performed at Screening, unless prohibited by local regulations. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.
- u. At Week 2 and Week 4 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.
- v. PK samples should be collected at any time during the visit. Subject should follow the regular dosing schedule.
- w. Samples only collected if subject provides written consent.
- x. 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 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.

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

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 14/PD
	D -35 to D -1	D1	D15	D29	D57	D99
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.

Appendix E. Study Activities (Period 2)

Activity	Wk 20	Wk 26	Wk 36	Wk 48	Every 12 Weeks ^a	Every 24 Weeks ^a	Monthly	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
Concomitant therapy	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	
Patient questionnaires ^d EQ-5D-5L SF-36				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				X ^f				X ^f		
12-lead ECG				X ^g				X ^g	X ^g	
Vital signs and body weight ^h	X	X	X	X	X				X	X
Physical exam		X				X ⁱ			X	
Physician Global Assessment (PhGA)	X	X	X	X	X				X	
TJC68/SJC66	X	X	X	X	X				X	

Activity	Wk 20	Wk 26	Wk 36	Wk 48	Every 12 Weeks ^a	Every 24 Weeks ^a	Monthly	Every 48 Weeks ^a	Final (Wk 260)/ PD Visit	30-Day F/U Visit ^b
20% joint assessment (TJC and SJC) ^j		X	X	X	X					
Local urine pregnancy test ^k	X	X	X	X	X				X	X
At-home urine pregnancy test							X ^k			
CDAI		X ^{l,m}								
Central lab tests hsCRP ⁿ Blood chemistry ^o Hematology (CBC) Urinalysis ^p	X	X	X	X	X				X	X
ESR (local lab)	X	X	X	X	X				X	
Dispense study drug and subject dosing diary		X	X	X	X					
Review and copy subject dosing diary and perform drug reconciliation	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 Assessment of 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 study drug for those subjects who complete 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.

- c. At Week 26 (after Week 26 assessments have been performed), per Investigator judgment, may add csDMARDs (concomitant use of up to 2 csDMARDs, except the combination of MTX and leflunomide). Subjects who do not achieve LDA as defined by $CDAI \leq 10$ at Week 26 should have background medication(s) adjusted or initiated as rescue after assessments for Week 26 have been finished.
- 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 TB tests, or per local guidelines. 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. Obtain chest x-ray every 48 weeks after Week 48 for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive TB test after baseline.
- g. ECGs will be performed every 48 weeks after Week 48. An ECG may be performed at any visit if deemed necessary by the Investigator.
- 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 26 and thereafter, study drug should be discontinued for subjects who fail to show at least 20% improvement in both TJC and SJC compared to baseline at 2 consecutive visits, despite optimization of background RA therapies.
- k. 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 the study. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.
- l. Refer to Section 5.2.3.1.
- m. CDAI calculation requires input of SJC + TJC (based on a 28 joint count) + PtGA + PhGA into IRT system.
- n. 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. For safety evaluations of signs and symptoms of infection and management of adverse events, the investigator may locally test procalcitonin. Results of tests such as hsCRP may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. Any local hsCRP or CRP tests should not be reported to the investigator until treatment allocation is unblinded or subject is known to be receiving upadacitinib. In Period 2, the central lab hsCRP results will remain blinded to Investigator, study site personnel, and the subject. Starting with Amendment 5, 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 Premature Discontinuation Visit (PD Visit) as soon as possible, preferably within 2 weeks. Refer to Section 5.1 Discontinuation of Study Drug and Continuation of Study Participation (Period 1 and Period 2) for additional details.

Appendix F. 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. 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 G. Joint Evaluation Worksheet Example

JOINT EVALUATION													
JOINT (Tick Correct Answer)	Subject Right						Subject Left						
	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment		
	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint		
	0	1	0	1	9	NA	0	1	0	1	9	NA	
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												
JOINT (Tick Correct Answer)	Subject Right						Subject Left					
	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
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. Interphalangeal I	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 H. 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 I. 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
Very Well

100
Very Poorly

Appendix J. 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 K. 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:

<u>WITHOUT ANY</u>	<u>WITH SOME</u>	<u>WITH MUCH</u>	<u>UNABLE</u>
DIFFICULTY	DIFFICULTY	DIFFICULTY	TO DO

DRESSING AND GROOMING

Are you able to:

Dress yourself, including tying shoelaces and doing buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
--	--------------------------	--------------------------	--------------------------	--------------------------

Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
--------------------	--------------------------	--------------------------	--------------------------	--------------------------

ARISING

Are you able to:

Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
---------------------------------	--------------------------	--------------------------	--------------------------	--------------------------

Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
------------------------	--------------------------	--------------------------	--------------------------	--------------------------

EATING

Are you able to:

Cut your own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
--------------------	--------------------------	--------------------------	--------------------------	--------------------------

Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
---	--------------------------	--------------------------	--------------------------	--------------------------

Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-------------------------	--------------------------	--------------------------	--------------------------	--------------------------

WALKING

Are you able to:

Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
-------------------------------	--------------------------	--------------------------	--------------------------	--------------------------

Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
----------------------	--------------------------	--------------------------	--------------------------	--------------------------

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

- | | |
|-------------------------------------|---|
| <input type="checkbox"/> Cane | <input type="checkbox"/> Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.) |
| <input type="checkbox"/> Walker | <input type="checkbox"/> Built up or special utensils |
| <input type="checkbox"/> Crutches | <input type="checkbox"/> Special or built up chair |
| <input type="checkbox"/> Wheelchair | <input type="checkbox"/> 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 WITH SOME WITH MUCH UNABLE
DIFFICULTY DIFFICULTY DIFFICULTY TO DO**

HYGIENE

Are you able to:

- | | | | | |
|----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Wash and dry your body? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Take a tub bath? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Get on and off the toilet? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

REACH

Are you able to:

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| Reach and get down a 5-pound object (such as a bag of sugar) from just above your head? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Bend down to pick up clothing from the floor? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

GRIP

Are you able to:

- | | | | | |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| Open car doors? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Open jars which have been previously opened? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Turn faucets on and off? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

ACTIVITIES

Are you able to:

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| Run errands and shop? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Get in and out of a car? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Do chores such as vacuuming or yard work? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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

- | | |
|--|--|
| <input type="checkbox"/> Raised toilet seat | <input type="checkbox"/> Bathtub bar |
| <input type="checkbox"/> Bathtub seat | <input type="checkbox"/> Long-handled appliances for reach |
| <input type="checkbox"/> Jar opener (for jars previously opened) | <input type="checkbox"/> Long-handled appliances in bathroom |
| | <input type="checkbox"/> Other (Specify: _____) |



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

Hygiene

Gripping and opening things

Reach

Errands and chores

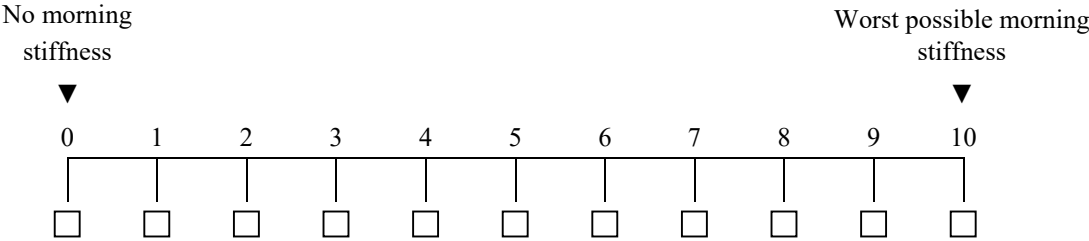
HAQ – United States/English

HAQ-DI_AU1.0-eng-USori.doc © Stanford University

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

Your Health and Well-Being

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

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

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

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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 <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d Climbing <u>several</u> flights of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e Climbing <u>one</u> flight of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f Bending, kneeling, or stooping	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g Walking <u>more than a mile</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h Walking <u>several hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i Walking <u>one hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j Bathing or dressing yourself	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 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

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^b Accomplished less than you would like

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^c Were limited in the kind of work or other activities

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^d Had difficulty performing the work or other activities (for example, it took extra effort)

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^b Accomplished less than you would like

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^c Did work or other activities less carefully than usual

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 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
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^b Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^d Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^e Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^f Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^g Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^h Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
ⁱ Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 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	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^b I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^c I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^d My health is excellent	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

THANK YOU FOR COMPLETING THESE QUESTIONS

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Appendix N. 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

Appendix O. Rheumatology Common Toxicity Criteria v.2.0 Example

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

Rheumatology Common Toxicity Criteria v.2.0				
Based on Woodworth TG, et al. Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for Anti-Rheumatic Therapies				
	1 – Mild	2 – Moderate	3 – Severe	4 – Includes Life Threatening
	Asymptomatic, or transient Short duration (< 1 week) No change in life style No medication or OTC	Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription) Study drug continued	Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation, or/and dose reduced	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	Serilogic 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 relieve	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 \geq 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, arrhythmia 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 pruritis; dry desquamation; treatment required	Generalised, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalisation; or parenteral corticosteroids
D9. Induration/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. Xerophthalmia (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)	Haemorrhoidal, 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 pancreatic 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				
11. 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
12. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events	Cerebrovascular vascular accident with permanent disability
13. 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
14. Depressed consciousness (somnia)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
15. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	NA
16. 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
17. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	NA
18. 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
19. 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 paraesthesias interfering with function	NA
110. 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 therefore 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.