



Upadacitinib  
M14-663 Protocol Amendment 5

## 1.0

## Title Page

# Clinical Study Protocol M14-663

## **A Phase 2b/3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs**

## **Incorporating Administrative Changes 1, 2, 3, and 4 and Amendments 1, 2, 3, and 5**

AbbVie  
Investigational  
Product:

Upadacitinib

Date:

23 February 2018

Development Phase:

2b/3

Study Design:

A 12-week randomized, double-blind, parallel-group, placebo-controlled period followed by a blinded long-term extension period

EudraCT Number:

N/A

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.**

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## 1.1 Protocol Amendment: Summary of Changes

### Previous Protocol Versions

Protocol	Date
Original	23 December 2015
Amendment 1	25 January 2016
Amendment 2	11 May 2016
Administrative Change 1	13 May 2016
Administrative Change 2	08 July 2016
Amendment 3	21 November 2016
Administrative Change 3	03 February 2017
Administrative Change 4	31 March 2017
Amendment 4 ( <i>withdrawn by the Sponsor</i> )	27 November 2017
Administrative Change 5 ( <i>withdrawn by the Sponsor</i> )	20 December 2017

The purpose of this amendment is to:

- Apply administrative changes throughout protocol.

**Rationale:** *Revised text to improve consistency and readability, and/or provide clarification.*

- Change ABT-494 to upadacitinib throughout the protocol

**Rationale:** *Revised to reflect the recently approved International Nonproprietary Name.*

- Update Section 1.0 "Title Page"

**Rationale:** *Change the Sponsor/Emergency Contact to Dr. [REDACTED] [REDACTED] to inform the sites of the change in contact for subject safety concerns and emergencies (as per Protocol Administrative Change 4).*

- Update Section 1.2, Synopsis.

**Rationale:** *Revised to be consistent with Amendment 5 revisions.*

- Update Section 1.3, List of Abbreviations.

**Rationale:** *Revised to be consistent with Amendment 5 revisions.*

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

**Rationale:** *Revised to be consistent with Amendment 5 revisions. Updated text to clarify the improvement required in both swollen joint count and tender joint count compared to baseline to remain in the study. Updated text to clarify that additional unblinded analyses will be performed for the purpose of regulatory submission in addition to the one conducted after all subjects have completed Period 1 (Week 12). Updated text to clarify that subjects that screen fail for re-tested exclusionary laboratory values may be re-screened after consultation with the AbbVie Therapeutic Medical Director (as per Protocol Administrative Change 3). Updated text in Subsections "Period 1" "Period 2" and "Premature Discontinuation of Study" to improve readability and provide clarity.*

- Update Section 5.2.3.2, Concomitant Therapy.

**Rationale:** *Updated text to provide clarity on csDMARDs that are allowed at Week 24 onwards if a subject fails to meet the LDA criterion for adjustment of subject's background RA therapies.*

- Update Section 5.2.3.3, Prohibited Therapy.

**Rationale:** *Updated Table 1, Examples of Commonly Used Strong CYP3A Inhibitors and Inducers, to add Rifapentine. Updated Subsection "Vaccines" to clarify that live vaccines are prohibited up to 30 days following last dose of study drug. Updated Subsection "Traditional Chinese Medicine" to clarify that traditional Chinese medicine taken orally is not permitted during the study.*

- Update Section 5.2.4, Contraception Recommendations.

**Rationale:** *Revised Subsection "Contraception Recommendation for Females" per sponsor guidelines to update the list of acceptable birth control methods for women of child bearing potential and clarify requirements for contraception for women if child-bearing potential status changes during the course of the study.*

*Revised Subsection "Contraception Recommendation for Males" per sponsor guidelines to clarify that contraception and sperm recommendations are specifically intended to prevent pregnancy during exposure to the investigational therapy.*

- Revise **Table 2**, Study Activities (Period 1) and Revise **Table 4**, Study Activities (Period 2).

**Rationale:** *Updated text to provide clarity on hsCRP reporting in Period 1 and 2, to provide additional instructions and to remain consistent with Amendment 5 changes reflected in the protocol.*

- Update Section **5.3.1.1**, Study Procedures, Subsection "TB Testing/TB Prophylaxis."

**Rationale:** *Revised text to prevent unnecessary initiation of TB prophylaxis in subjects with indeterminate QuantiFERON-TB test results by allowing local testing. Revised to include Rifapentine as excluded medication for TB prophylaxis and to provide clarity on TB testing and TB prophylaxis in Period 2.*

- Update Section **5.3.1.1**, Study Procedures, Subsection "Chest X-ray."

**Rationale:** *Revised text to clarify that a pulmonologist may also perform assessment of Chest X-ray and to remove the requirement of Chest X-ray at Final/Premature Discontinuation visit in Period 2.*

- Update Section **5.3.1.1**, Study Procedures, Subsection "12-Lead ECG."

**Rationale:** *Revised text to clarify QTcF calculation procedures.*

- Update Section **5.3.1.1**, Study Procedures, Subsection "Pregnancy Test."

**Rationale:** *Revised text to remove required pregnancy test for women who become post-menopausal or surgically sterile during the study and to clarify procedures in case urine pregnancy test post-baseline is positive.*

- Update Section **5.3.1.1**, Study Procedures, Subsection "Clinical Laboratory Tests."

**Rationale:** *Updated footnotes of Table 5 to provide clarity, additional instructions and to remain consistent with Amendment 5 changes reflected in the protocol.*

- Update Section **5.3.1.1**, Study Procedures, Subsection "Hepatitis Screen."

**Rationale:** *Updated text to clarify Hepatitis B testing requirements for HBV-DNA PCR testing. Updated text to clarify the management of subjects who develop positive result for HBV DNA PCR testing during the study,*

*including hepatologist consultation and possible study drug interruption per local guidelines.*

- Update Section 5.3.3.1.3, Additional Variables

**Rationale:** *Added change from baseline in FACIT-F and RA-WIS for all visits.*

- Update Section 5.4.1, Discontinuation of Individual Subjects.

**Rationale:** *Updated text to clarify that starting at Week 24, at least 20% improvement in both swollen joint counts and tender joint counts compared to baseline is required to remain in the study. Updated text to remove the discontinuation criterion related to the study drug interruption during the study.*

- Update Section 5.5.5.2, Identity of Investigational Product.

**Rationale:** *Updated to clarify the formulation of upadacitinib.*

- Update Section 5.5.5, Blinding of Investigational Product.

**Rationale:** *Updated text to clarify that additional unblinded analyses will be performed for the purpose of regulatory submission in addition to the one conducted after all subjects have completed Period 1 (Week 12).*

- Update Section 6.1.1.3, Adverse Events of Special Interest

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

- Update 6.1.3 Relationship to Study Drug

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

- Update Section 6.1.4, Adverse Event Collection Period

**Rationale:** *Updated text to implement supplemental eCRF for embolic and thrombotic events.*

- Update Section 6.1.5, Serious Adverse Event Reporting

**Rationale:** *Change the Sponsor/Emergency Contact to Dr. [REDACTED] to inform the sites of the change in contact for subject safety*

*concerns and emergencies (as per Protocol Administrative Change 4).*

*Updated regulations governing SUSARs reporting.*

- Update Section [6.1.7](#), Toxicity Management.

**Rationale:** *Removed the requirement to discontinue subjects who experience serious infections and have interrupted study drug for more than 7 consecutive days during the first 24 weeks of the study or 30 consecutive days thereafter in order to be consistent with Section [5.4.1](#) which requires discontinuation of study drug for serious infections which cannot be adequately controlled within 14 days by anti-infective treatment. Clarified that subject should discontinue study drug for an ECG abnormality that is considered clinically significant with reasonable possibility that the event is related to study drug. Clarified that all abnormal lab tests that are considered clinically significant by the investigator should be followed to a satisfactory resolution. Updated [Table 7](#) "Specific Toxicity Management Guidelines for Abnormal Laboratory Values" to provide clarity and additional instructions for management of increased ALT/AST, Serum Creatinine and Creatine Phosphokinase.*

- Update Section [6.2.2](#), Reporting

**Rationale:** *Updated text to define Product Complaint reporting timeline as 1 business day.*

- Update Section [8.1](#) Statistical and Analytical Plans.

**Rationale:** *Updated text to clarify that additional unblinded analyses will be performed for the purpose of regulatory submission in addition to the one conducted after all subjects have completed Period 1 (Week 12).*

- Update Section [8.1.4.1.5](#) Imputation Methods.

**Rationale:** *Updated language for analysis details.*

- Update Section [8.1.5.2.1](#), Treatment-Emergent Adverse Events (TEAE)

**Rationale:** *Updated search criteria for the AEs of special interest (AESI) categories.*

- Update Section [8.1.5.3](#) Analysis of Laboratory, Vital Sign, and ECG Data.

**Rationale:** *Updated language for analysis details.*

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

***Rationale:*** *Updated signatories responsible for the amendment.*

- Update [Appendix N](#), Rheumatology Common Toxicity Criteria v.2.0 Example.

***Rationale:*** *Updated to clarify grading criteria for CPK and Creatinine.*

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

## 1.2 Synopsis

<b>AbbVie GK.</b>	<b>Protocol Number:</b> M14-663
<b>Name of Study Drug:</b> Upadacitinib	<b>Phase of Development:</b> 2b/3
<b>Name of Active Ingredient:</b> Upadacitinib	<b>Date of Protocol Synopsis:</b> 23 February 2018
<b>Protocol Title:</b> A Phase 2b/3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs	
<b>Objectives:</b>	
<b>Period 1</b>	
1. To confirm dose response in the efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD, and to compare the efficacy of upadacitinib versus placebo for the treatment of signs and symptoms of Japanese subjects with moderately to severely active rheumatoid arthritis (RA) who are on a stable dose of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and have an inadequate response to csDMARDs.	
2. To compare the safety and tolerability of upadacitinib 7.5 mg QD, 15 mg QD and 30mg QD versus placebo in Japanese subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.	
<b>Period 2</b>	
To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.	
<b>Investigators:</b> Multicenter	
<b>Study Sites:</b> Approximately 52	
<b>Study Population:</b> Adult female and male subjects who are at least 18 years of age with a diagnosis of RA for $\geq$ 3 months who also fulfill the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have $\geq$ 6 swollen joints (based on 66 joint counts) and $\geq$ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP) $\geq$ 3 mg/L (central lab) at Screening. Subjects must have been on a stable dose of csDMARD therapy (methotrexate [MTX], sulfasalazine, leflunomide, bucillamine or iguratimod) for $\geq$ 4 weeks prior to the first dose of study drug.	
<b>Number of Subjects to be Enrolled:</b> Approximately 192	
<b>Methodology:</b>	
This is a Phase 2b/3 multicenter study that includes two periods. Period 1 is a 12-week randomized, double-blind, parallel-group, placebo-controlled period designed to confirm dose response in the efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD and to compare the safety and efficacy of upadacitinib versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.	

**Methodology (Continued):**

The study duration will include a 35-day screening period; a 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a blinded long-term extension period (until regulatory approval of RA indication in Japan) (Period 2); and a 30-day follow-up period. Subjects who meet eligibility criteria will be randomized in a 3:3:3:1:1:1 ratio to one of six treatment groups:

- Group 1: upadacitinib 7.5 mg QD (N = 48) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 2: upadacitinib 15 mg QD (N = 48) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 3: upadacitinib 30 mg QD (N = 48) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → upadacitinib 30 mg QD (Period 2)

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

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

Starting at Week 24 (after Week 24 assessments have been performed), initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, low potency analgesics or csDMARDs (restricted to oral or parenteral MTX, sulfasalazine, leflunomide, bucillamine or iguratimod and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label. Starting at Week 24, at least 20% improvement in BOTH SJC AND TJC compared to baseline is required to remain in the study. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) (see Section 5.2.3.2 for permitted concomitant therapy), must be discontinued from the study. For RA flare treatment, no more than 3 consecutive days of systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Subjects taking MTX should take oral folic acid throughout study participation. Folic acid dosing and timing of regimen will be based on the Investigator's discretion.

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

Subjects who complete the Week 12 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2, until the regulatory approval of the RA indication in Japan. Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner.

**Methodology (Continued):**

Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission will be conducted. Study sites and subjects will remain blinded for the duration 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  $\geq$  3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects have been receiving csDMARD therapy  $\geq$  3 months and on a stable dose for  $\geq$  4 weeks prior to the first dose of study drug.
  - Subjects must have failed (lack of efficacy) at least one of the following: MTX, sulfasalazine, leflunomide, bucillamine or iguratimod.
  - The following csDMARDs are allowed (stable dose for  $\geq$  4 weeks prior to the first dose of study drug): oral or parenteral MTX (7.5 mg – 25 mg/week. 7.5 mg minimum applies only if MTX is taken alone without other csDMARDs; no minimum MTX dose is required if MTX is combined with another csDMARD), sulfasalazine ( $\leq$  3000 mg/day), leflunomide ( $\leq$  20 mg/day), bucillamine ( $\leq$  300 mg/day) and iguratimod ( $\leq$  50 mg/day).
  - A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
4. Subject meets both of the following disease activity criteria:
  - a.  $\geq$  6 swollen joints (based on 66 joint counts) and  $\geq$  6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
  - b. High-sensitivity C-reactive protein (hsCRP)  $\geq$  3 mg/L (central lab) at the Screening Visit.
5. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of total number of subjects) after the required washout period. Specifically, prior to enrollment:
  - a. Subjects with limited exposure to bDMARD ( $<$  3 months) OR
  - b. Subjects who are responding to bDMARD therapy but had to discontinue due to intolerance (regardless of treatment duration).

**Main Exclusion:**

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Subjects who are considered inadequate responders (lack of efficacy) to bDMARD therapy, after minimum 3 months treatment, as determined by the Investigator.
3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis [SpA] 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.

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

4. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase  $> 2 \times$  upper limit of normal (ULN); serum alanine transaminase  $> 2 \times$  ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula  $< 40 \text{ mL/min}/1.73 \text{ m}^2$ ; total white blood cell count  $< 2,500/\mu\text{L}$ ; absolute neutrophil count  $< 1,500/\mu\text{L}$ ; platelet count  $< 100,000/\mu\text{L}$ ; absolute lymphocyte count  $< 800/\mu\text{L}$ ; and hemoglobin  $< 10 \text{ g/dL}$ .

**Investigational Product:** Upadacitinib**Doses:**  
7.5 mg QD  
15 mg QD  
30 mg QD**Mode of Administration:** Oral**Reference Therapy:** Matching placebo for upadacitinib QD**Dose:** N/A**Mode of Administration:** Oral**Duration of Treatment:** Period 1: 12 weeks; Period 2: up to the regulatory approval of RA indication in Japan**Criteria for Evaluation:****Efficacy:****Period 1**

The primary endpoint is the proportion of subjects achieving ACR20 response at Week 12.

ACR20 response rate will be determined based on 20% or greater improvement in Tender Joint Count (TJC) and Swollen Joint Count (SJC) and  $\geq 3$  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.

Key Secondary endpoints (at Week 12) are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. ACR50 response rate;
4. ACR70 response rate;
5. Change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS);
6. Proportion of subjects achieving Low Disease Activity (LDA) defined as Disease Activity Score (DAS) 28 (C-reactive protein [CRP])  $\leq 3.2$ ;
7. Proportion of subjects achieving Clinical remission (CR) based on DAS28 (CRP);
8. ACR20 response rate at Week 1;
9. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F);
10. Change from baseline in Work Instability Scale for Rheumatoid Arthritis (RA-WIS);
11. Change from baseline in morning stiffness (severity).

**Criteria for Evaluation (Continued):****Efficacy (Continued):**

Additional endpoints at all visits of this study are:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in morning stiffness (severity and duration);
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria (see below);
- Change from baseline in EQ-5D-5L;
- Change from baseline in SF-36;
- Change from baseline in FACIT-F;
- Change from baseline in RA-WIS.

	<b>DAS28 (CRP) and DAS28 (ESR)</b>	<b>SDAI</b>	<b>CDAI</b>
LDA	$\leq 3.2$	$\leq 11.0$	$\leq 10$
CR	$< 2.6$	$\leq 3.3$	$\leq 2.8$

**Period 2**

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 16, 20, 24, 36, 48, and every 12 weeks thereafter until completion of the study:

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

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

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

**Criteria for Evaluation (Continued):****Pharmacokinetic:**

Blood samples for assay of upadacitinib and possibly other concomitant medications in plasma will be collected at Weeks 1, 2, 4, 8 and 12/Premature Discontinuation in Period 1. Additionally, intensive pharmacokinetic assessment will be performed in approximately 32 subjects during one of the study visits, including unscheduled visits occurring after Week 1, in either Periods 1 or 2 excluding Baseline and Premature Discontinuation visit. For Subjects in the intensive pharmacokinetic assessment, blood samples will be collected during the study visit chosen for intensive pharmacokinetic (PK) assessment prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose.

**In Vivo Pharmacodynamic Biomarkers (Period 1 and 2)****Period 1**

Change from baseline in lymphocyte subsets (including but not limited to natural killer cells, natural killer T cells, B cells, and T cells) will be evaluated at Baseline, Week 8, Premature Discontinuation visit and 30 days follow-up visit.

**Period 2**

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

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

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

**Safety:**

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

**Statistical Methods:****Efficacy:**

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, and efficacy analyses are based on the treatment to which subjects are randomized.

**Period 1 Efficacy****Analysis of the Primary and Key Secondary Endpoints:****Primary Efficacy Analysis:**

The dose-response relationship among the upadacitinib groups and the combined placebo group will be characterized for the ACR20 response rate at Week 12. The dose-response curve will be shown graphically with confidence intervals for each dose and a non-flat dose response relationship will be demonstrated using Cochran-Armitage test. The response rates of ACR20 of each upadacitinib group will be compared with the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for main stratification factors.

**Key Secondary Efficacy Analysis:**

The key secondary efficacy endpoints (at Week 12) will be evaluated. For a list of the key secondary endpoints, see "Efficacy" part in "Criteria for Evaluation."

All nominal statistical comparisons of upadacitinib versus placebo for the primary and key secondary endpoints and for the three doses will be conducted using a two-sided significance level of 0.05.

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

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between each of the upadacitinib treatment groups and the combined placebo groups will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates.

Non-responder imputation approach will serve as the primary analysis approach for key binary endpoints, and multiple imputation will serve as the primary analysis approach for key continuous endpoints.

Sensitivity analyses based on observed cases 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.

**Statistical Methods (Continued):****Pharmacokinetic:**

A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of ABT-494 oral clearance (CL/F) and volume of distribution (V/F).

For the subjects participating in the intensive pharmacokinetic assessment, the following upadacitinib parameters will be estimated using noncompartmental methods:

- The maximum observed concentration ( $C_{\max}$ ),
- The time to  $C_{\max}$  (peak time,  $T_{\max}$ ),
- The area under the plasma concentration-time curve (AUC),
- The apparent oral clearance (CL/F),
- Plasma concentration at the end of dosing interval ( $C_{\text{trough}}$ )
- The minimum plasma concentration over a 24-hour period at steady state ( $C_{\min}$ )

Additional parameters may be estimated if useful in the interpretation of the data.

**Safety:**

Safety analyses will be carried out using the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug. Analyses will be conducted for Period 1 alone, as well as for Period 1 and Period 2 combined.

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

## 1.3 List of Abbreviations and Definition of Terms

### Abbreviations

ACR	American College of Rheumatology
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-CCP	anti-cyclic citrullinated peptide
AST	aspartate transaminase
AUC	area under the plasma concentration-time curve
BCG	Bacille Calmette-Guérin
bDMARD	biological disease-modifying anti-rheumatic drug
BID	twice daily (Latin: bis in die)
BUN	blood urea nitrogen
CBC	complete blood count
CD4, CD8	cluster of differentiation
CDAI	clinical disease activity index
CL/F	apparent oral clearance
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CPK	creatine phosphokinase
CR	clinical remission
CRF	case report form
CRP	C-reactive protein
C <sub>trough</sub>	plasma concentration at the end of the dosing interval
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CSR	clinical study report
CXR	chest x-ray
CYP	cytochrome
DAS	disease activity score
DMARD	disease-modifying anti-rheumatic drug
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid

ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL-5D-5L
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBc Ab/anti-HBc	Hepatitis B core antibody
HBs Ab/anti-HBs	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
INR	international normalized ratio
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
MRB	Minimal Residual B-cells
MTX	methotrexate
MTX-IR	methotrexate inadequate responder
NA	no assessment
NK	natural killer
NKT	natural killer-T
NMSC	non-melanoma skin cancer
NONMEM	non-linear mixed-effects modeling
NRI	non-responder imputation
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
OC	observed cases
OLE	open-label extension
PCR	polymerase chain reaction
PCS	physical component score
PD	premature discontinuation
PhGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic
PPD	purified protein derivative
PRN	as needed (Latin: pro re nata)
PRO	patient-reported outcome
PT	preferred term
PtGA	Patient's Global Assessment of Disease Activity
QD	once daily (Latin: quaque die)
RA	rheumatoid arthritis
RA-WIS	Work Instability Scale for Rheumatoid Arthritis
RAVE <sup>®</sup>	EDC system from Medidata
RBC	red blood cell
RCT	randomized controlled trial

RNA	Ribonucleic acid
SAA	serum-amyloid A
SAE	serious adverse event
SAP	statistical analysis plan
SDAI	Simple Disease Activity Index
SF-36	Short Form-36
SJC	swollen joint count
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T2T	treat-to-target
TA	Therapeutic Area
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
T <sub>max</sub>	time to maximum observed plasma concentration
TNF	tumor necrosis factor
TNF-IR	tumor necrosis factor inadequate responder
Tyk2	Tyrosine kinase 2
ULN	upper limit of normal
V/F	apparent volume of distribution
VAS	visual analog scale
WBC	white blood cell

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### 3.0                   Introduction

#### **Rheumatoid Arthritis**

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

The European League Against Rheumatism (EULAR) recommends a Treat-to-Target (T2T) approach to initiate therapy immediately after diagnosis of RA with a goal of achieving clinical remission (CR) or low disease activity (LDA), as these are associated with improved long-term outcomes.<sup>1-3</sup> 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.<sup>4</sup>

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.<sup>5,6</sup> Novel therapies are therefore needed to complement the available interventions to address the unmet need.<sup>5-7</sup>

## **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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10-14</sup> 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.<sup>8</sup> Upadacitinib is a novel selective JAK1 inhibitor being developed for the treatment of adult patients with moderately to severely active RA. In an in vitro setting, upadacitinib potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit-risk profile in patients with RA. The clinical hypothesis is that upadacitinib should be effective in decreasing joint

inflammation and damage associated with RA by interfering with JAK1-mediated signaling pathways (i.e., interleukin-6) without causing excessive anemia due to its reduced activity against JAK2 ( $IC_{50}$  120 nM), which is essential for erythropoietin signaling. Upadacitinib is also less potent against JAK3 ( $IC_{50}$  2.3  $\mu$ M), 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 Stage IIA lung adenocarcinoma after the final scheduled visit, and subsequently died 14 weeks after study completion. This subject had a 40 pack-year smoking history and a family history of cancer. 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 (maximum reduction of 0.89 g/dL in 18 mg BID group).

The once-daily formulation (tablet) of 7.5 mg, 15 mg and 30 mg QD doses to be used in this study are expected to have comparable daily AUC and  $C_{trough}$  to the 3 mg BID, 6 mg BID and 12 mg BID immediate release doses (capsule) used in the global Phase 2 studies, respectively.

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### **3.1 Differences Statement**

Study M14-663 differs from other upadacitinib studies as it is the first study to evaluate the safety and efficacy of upadacitinib in the Japanese csDMARD inadequate responder population.

### **3.2 Benefits and Risks**

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

## **4.0 Study Objectives**

### **Period 1**

1. To confirm dose response in the efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD, and to compare the efficacy of upadacitinib versus placebo for the treatment of signs and symptoms of Japanese subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.
2. To compare the safety and tolerability of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD versus placebo in Japanese subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.

**Period 2**

To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 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 2b/3 multicenter study that includes two periods. Period 1 is a 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.

The study duration will include a 35-day screening period; a 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a blinded long-term extension period (until regulatory approval of RA indication in Japan) (Period 2); and a 30-day follow-up period (call or visit).

The study is designed to enroll approximately 192 subjects at approximately 52 study centers in Japan to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Subjects who meet eligibility criteria will be randomized in a 3:3:3:1:1:1 ratio to one of six treatment groups:

- Group 1: Upadacitinib 7.5 mg QD (N = 48) (Period 1) → Upadacitinib 7.5 mg QD (Period 2)

- Group 2: Upadacitinib 15 mg QD (N = 48) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 3: Upadacitinib 30 mg QD (N = 48) (Period 1) → Upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → Upadacitinib 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → Upadacitinib 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → Upadacitinib 30 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/no).

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

At Week 24, if a subject fails to meet the Low Disease Activity (LDA) criterion (LDA defined as CDAI  $\leq$  10), the investigator should adjust the subject's background RA therapies. Starting at Week 24 (after Week 24 assessments have been performed), initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or adding or increasing doses of csDMARDs (concomitant use of up to csDMARDs except the combination of MTX and leflunomide) is allowed as per local label. Starting at Week 24, at least 20% improvement in BOTH SJC AND TJC compared to baseline is required to remain in the study. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) (see Section [5.2.3.2](#) for concomitant therapy) must be discontinued from the study.

Subjects taking MTX should take oral folic acid throughout study participation. Folic acid dosing and timing of regimen will be based on the Investigator's discretion.

Subjects with prior exposure to at most one bDMARD for RA may be enrolled in the study (up to 20% of total number of subjects) after the required washout period is satisfied **and if** they have limited exposure to bDMARD (< 3 months) OR response to bDMARD but had to discontinue that bDMARD due to intolerance (regardless of treatment

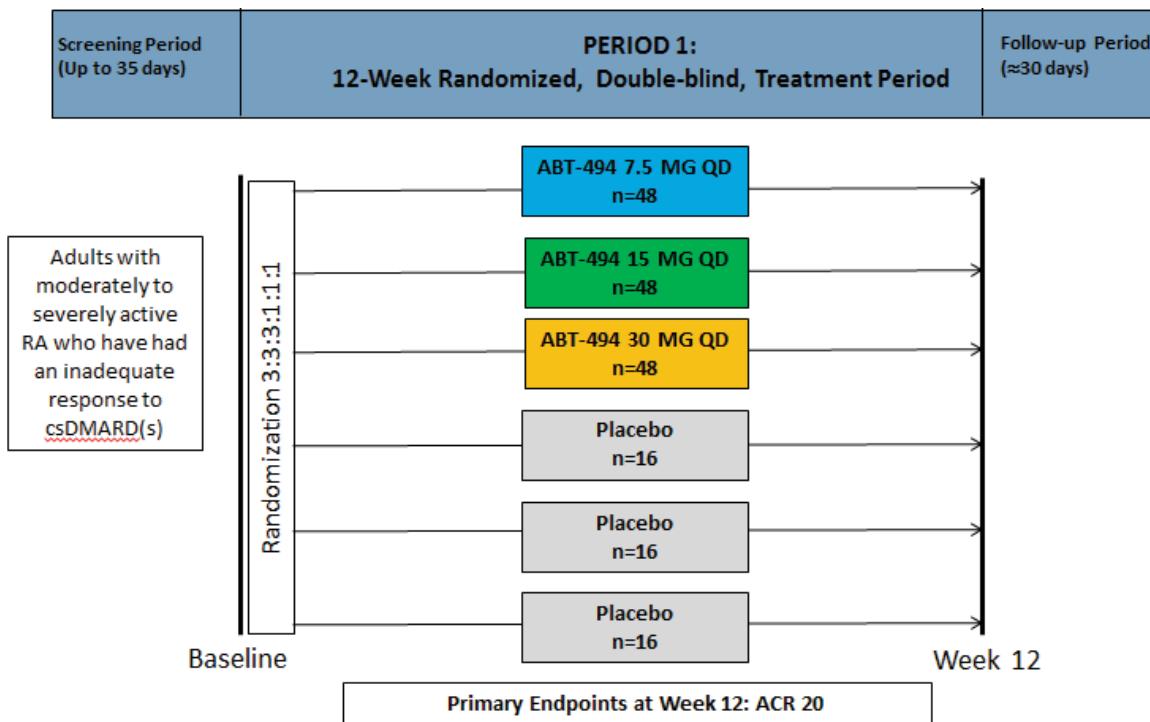
duration) (for washout periods, see Inclusion Criterion 7, Section [5.2.1](#)). These subjects will be equally stratified across all treatment groups. Subjects who are considered bDMARD inadequate responders, as determined by the Investigator, are not eligible.

Subjects who complete the Week 12 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2, until the regulatory approval of the RA indication in Japan. Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission will be conducted.

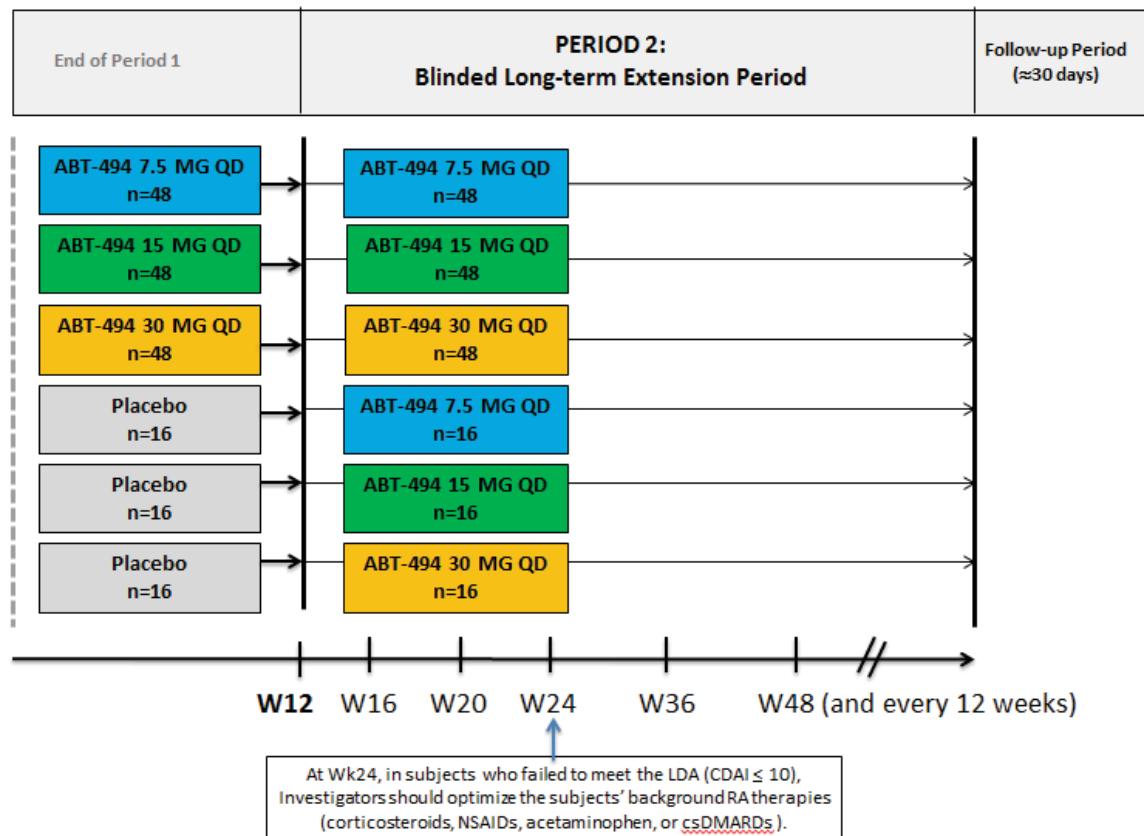
Study sites and subjects will remain blinded throughout Periods 1 and 2.

Schematics of Periods 1 and Period 2 are shown in [Figure 1](#) and [Figure 2](#), respectively.

**Figure 1. Period 1 Study Design**

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

The follow-up period is for subjects who do not enter Period 2 or prematurely discontinued study drug and study participation.

**Figure 2. Period 2 Study Design**

CDAI = clinical disease activity index; csDMARD = conventional synthetic disease modifying anti-rheumatic drug; LDA = low disease activity; QD = once daily; Wk = week

The follow-up period is for subjects who complete Period 2 or prematurely discontinued study drug and study participation.

### Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in [Table 2](#). Lab values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Subjects that screen fail for re-tested laboratory values may be re-screened only after consultation with the AbbVie TA MD.

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

Subjects that initially screen fail (for reasons other than re-tested laboratory values) for the study are permitted to re-screen once following re-consent. For additional re-screening, AbbVie Therapeutic Area Medical Director (TA MD) approval is required. All screening procedures with the possible exceptions noted below will be repeated during re-screening. The subject must meet all the inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) and/or a purified protein derivative (PPD) test (or equivalent) (or both if required per local guidelines), or chest x-ray and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met, there are no changes in the subject's medical history that would warrant re-testing, and no more than 90 days have passed.

### **Period 1 (12-Week Randomized, Double-Blind Treatment Period)**

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 12 Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the study and randomized to double-blind treatment. During this period of the study, subjects will visit the study site at Weeks 1, 2, 4, 8 and 12. A  $\pm$  3 day window is permitted around scheduled study visits. The last dose of study drug is taken the day prior to the Week 12 visit. Subjects who complete Period 1, but decide not to continue in Period 2 should complete a 30 day follow-up visit after the last dose of study drug.

### **Period 2 (Blinded Long-Term Extension Period [up to Regulatory Approval of the RA Indication in Japan])**

Period 2 will begin at the Week 12 visit after all assessments have been completed. During Period 2, subjects will have a study visit at Weeks 16, 20, 24, 36, 48, and every

12 weeks thereafter until completion of the study. A  $\pm$  7 day window is permitted around scheduled study visits. At Week 24, if a subject fails to meet LDA criterion (LDA defined as CDAI  $\leq$  10) investigator should adjust the subject's background RA therapies. Starting at Week 24 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain in the study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24), despite optimization of background RA therapies (see Section 5.2.3.2) must be discontinued from the study.

### **Premature Discontinuation of Study (Withdrawal of Informed Consent)**

Subjects may withdraw from the study (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.

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 Period**

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

Subjects will complete the 30 day-Follow-Up Visit when they have either:

- Completed the last visit of Period 1 (Week 12), but decided not to participate in Period 2; OR
- Completed the last visit of Period 2; OR

- Prematurely discontinued study drug and study participation. If a Premature Discontinuation visit has already occurred, then the 30 day Follow-Up visit may be a telephone call if a site visit is not possible.

## **5.2 Selection of Study Population**

It is anticipated that approximately 192 subjects with moderately to severely active RA will be randomized at approximately 52 study centers in Japan.

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  $\geq$  3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects have been receiving csDMARD therapy  $\geq$  3 months and on a stable dose for  $\geq$  4 weeks prior to the first dose of study drug.
  - Subjects must have failed (lack of efficacy) at least one of the following: MTX, sulfasalazine, leflunomide, bucillamine or iguratimod.
  - The following csDMARDs are allowed (stable dose for  $\geq$  4 weeks prior to the first dose of study drug): oral or parenteral MTX (7.5 mg – 25 mg/week. 7.5 mg minimum applies only if MTX is taken alone without other csDMARDs; no minimum MTX dose is required if MTX is combined with another csDMARD), sulfasalazine ( $\leq$  3000 mg/day), leflunomide ( $\leq$  20 mg/day), bucillamine ( $\leq$  300 mg/day) and iguratimod ( $\leq$  50 mg/day).
  - A combination of up to two csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
4. Subject meets both of the following disease activity criteria:

- a.  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
  - b. hsCRP  $\geq 3$  mg/L (central lab) at the Screening Visit.
5. Stable dose of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen/paracetamol must have been at a stable dose  $\geq 1$  week prior to the first dose of study drug; oral corticosteroids (equivalent to prednisone  $\leq 10$  mg/day), or inhaled corticosteroids for stable medical conditions are allowed but must have been at a stable dose  $\geq 4$  week prior to the first dose of study drug.
6. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of total number of subjects). Specifically, prior to enrollment:
  - a. Subjects with limited exposure to bDMARD (< 3 months) OR
  - b. Subjects who are responding to a bDMARD therapy but had to discontinue due to intolerance (regardless of treatment duration).
7. Subjects must have discontinued bDMARD therapy prior to the first dose of study drug. The washout period for bDMARDs prior to the first dose of study is specified below or at least five times the mean terminal elimination half-life of a drug:
  - $\geq 4$  weeks for etanercept;
  - $\geq 8$  weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, and tocilizumab;
  - $\geq 1$  year for rituximab OR  $\geq 6$  months if B cells have returned to pre-treatment level or normal reference range (central lab) if pre-treatment levels are not available.
  - For all other bDMARDS, contact the TA MD for the washout period required prior to the first dose of study drug.
8. Subjects with prior exposure to immunosuppressant may be enrolled if completed the washout period as specified below:

- $\geq 4$  weeks prior to first dose of study drug for tacrolimus, azathioprine, cyclosporine, or mizoribine.

9. Subjects must have discontinued all high-potency opiates at least 1 week prior to the first dose of study drug and traditional Chinese medicine for at least 4 weeks prior to the first dose of study drug (refer to Section 5.2.3.3 for prohibited medications).
10. If female, subject must be either postmenopausal, OR permanently surgically sterile, OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.
11. If the male subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through at least 30 days after the last dose of study drug, to practice the protocol specified contraception (Section 5.2.4).
12. Women of childbearing potential must not have a positive pregnancy test result at Screening or Baseline visits. *Note: subjects with borderline pregnancy test at Screening must have a serum pregnancy test  $\geq 3$  days later to document continued lack of a positive result.* Women of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.
13. Male subjects, including those who have had a vasectomy less than 6 months earlier, should use a condom from the time of the first dose of study drug administration until 30 days after the last dose of study drug. Men who have had a vasectomy greater than 6 months prior to the first dose of study drug are not required to use a condom. Men must not donate sperm for at least 30 days after last dose of study drug.
14. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. In case of the subjects

under 20 years of age, the subjects, and their parents or legal guardian must voluntarily sign and date an informed consent.

### **Rationale for Inclusion Criteria**

- 1 – 9              To select the appropriate subject population
- 10 – 13            Upadacitinib is teratogenic in both rats and rabbits. The effect of upadacitinib on pregnancy and reproduction is unknown
- 14                  In accordance with harmonized Good Clinical Practice (GCP)

### **5.2.2              Exclusion Criteria**

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

- 1. Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
- 2. Subjects who are considered inadequate responders (lack of efficacy) to bDMARDs therapy, after at minimum 3 months treatment, as defined by the Investigator.
- 3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis (SpA) 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.
- 4. Has been treated with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the preceding 8 weeks prior to the first dose of study drug.

5. Has been treated with any investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.
6. Female who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
7. Male subject who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last does of study drug.
8. Any active or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or known history of human immunodeficiency virus (HIV). Active HBV, and HCV are defined as:
  - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects or hepatitis surface antibody (HBs Ab) positive (+) subjects;
  - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
9. Subject has active TB or meets TB exclusionary parameters (refer to Section [5.3.1.1](#) for specific requirements for TB testing).
10. Systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to [Table 1](#) for examples of commonly used strong CYP3A inhibitors and inducers).
11. Receipt of any live vaccine within 8 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 8 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 gastrointestinal 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. Clinically relevant of significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF)  $> 500$  msec.
18. History of clinically significant medical conditions or any other reason that in the opinion of the Investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
19. Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug.
20. History of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
21. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST)  $> 2 \times$  ULN
  - Serum alanine transaminase (ALT)  $> 2 \times$  ULN
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula  $< 40$  mL/min/1.73 m<sup>2</sup>
  - Total white blood cell (WBC) count  $< 2,500/\mu\text{L}$

- Absolute neutrophil count (ANC) < 1,500/ $\mu$ L
- Platelet count < 100,000 / $\mu$ L
- Absolute lymphocyte count < 800/ $\mu$ L
- Hemoglobin < 10 g/dL

22. History of any of the following cardiovascular conditions:

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

23. Positive result of beta-D-glucan or two consecutive indeterminate results of beta-D-glucan.

24. Subject with any planned (elective) surgery within the first 12 weeks of the study.

### **Rationale for Exclusion Criteria**

1 – 4	To select the appropriate subject population
6, 7	The impact of upadacitinib on pregnancies is unknown
5, 8 – 24	To ensure safety of the subjects throughout the study

#### **5.2.3 Prior, Concomitant, and Prohibited Therapy**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements including folic acid) that the subject is receiving at the time of enrollment, 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. 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 TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

#### **5.2.3.1            Prior Therapy**

Subjects should continue on their stable ( $\geq 4$  weeks prior to the first dose of study drug) dose of csDMARD therapy (restricted to oral or parenteral MTX [7.5 mg – 25 mg/week – 7.5 mg minimum applies only if MTX is taken alone without other csDMARDs], sulfasalazine [ $\leq 3000$  mg/day], leflunomide [ $\leq 20$  mg/day], bucillamine [ $\leq 300$  mg/day], or iguratimod [ $\leq 50$  mg/day]) up to Week 24. A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide. For subjects that are taking a combination of MTX and leflunomide therapy, discontinuation of either MTX or leflunomide should occur prior to the first dose of study drug (refer to csDMARD Washout below). At any time, the csDMARD dose may be decreased only for safety reasons. Subjects taking MTX should take oral folic acid (or equivalent, such as folinic acid) throughout study participation. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions. AbbVie will not provide the csDMARDs (or folic acid, if taking MTX).

#### **csDMARD Washout**

The following washout period should be met for subjects who are being treated with multiple csDMARDs and if washout of a csDMARD is required to meet the protocol requirements:

- $\geq 4$  weeks prior to the first dose of study drug for MTX, minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, cyclosporine, tacrolimus, mizoribine, gold formulations, cyclophosphamide.
- $\geq 8$  weeks prior to the first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to a washout procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal)

- $\geq$  five times the mean terminal elimination half-life for any other csDMARDs not listed above.

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

### **5.2.3.2 Concomitant Therapy**

The following medications are allowed: NSAIDs, acetaminophen/paracetamol, oral corticosteroids (equivalent to prednisone  $\leq$  10 mg/day), or inhaled corticosteroids.

- If taking any of the above medications on a scheduled basis, subject should continue to take them as done at study entry with no change in dose or frequency, including on study visit days (see Inclusion Criterion 5).
- If not taking any of the above medications at baseline, these must not be initiated except where permitted by protocol (after Week 24 assessments have been performed);
- If taking any of the above medications including low potency analgesics, i.e., tramadol, codeine, hydrocodone or propoxyphene at baseline on an as-needed basis (PRN), subject should continue to use them but these medications 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 dose of these medications may be decreased or discontinued with substitution of another permitted medication from that class (see Section 5.2.3.3 for prohibited therapies). PRN use of inhaled corticosteroids is permitted at any time.

At Week 24 (after Week 24 assessments have been performed) if a subject fails to meet the LDA criterion (LDA defined as CDAI  $\leq$  10), the investigator should adjust the subject's background RA therapies. Initiation of or change in corticosteroids, NSAIDs, acetaminophen/paracetamol, low potency analgesics, or csDMARDs (restricted to oral or parenteral MTX, sulfasalazine, leflunomide, bucillamine or iguratimod and restricted to

concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 3) is allowed as per local label. Starting at Week 24 and thereafter, intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids, dosage and frequency per standard of care, are allowed. However, joint injections should be avoided within 21 days prior to the next scheduled study visit to avoid confounding effects of systemic absorption of intra articular corticosteroids. For the analysis of the TJC and SJC, injected joints will be considered "not assessable" for 3 months from the time of the intra-articular injection. Also, per investigator's judgment, background RA therapies (corticosteroids, NSAIDs, acetaminophen, csDMARDs) can be adjusted for each subject beyond Week 24 until end of Period 2. For RA flare treatment, no more than 3 consecutive days of high-dose systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

### **5.2.3.3 Prohibited Therapy**

#### **JAK Inhibitor**

Prior exposure to JAK inhibitors (including but not limited to tofacitinib [Xeljanz<sup>®</sup>], baricitinib, and 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 24.

#### **Biologic Therapies**

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

Subjects with prior exposure to at most one bDMARD for RA may be enrolled in the study (up to 20% of study total number of subjects) after the required washout period is satisfied and if they have a) limited bDMARD exposure (< 3 months), OR b) response to

a bDMARD but had to discontinue that bDMARD due to intolerance (regardless of treatment duration).

Subjects must have discontinued all bDMARDs prior to the first dose of study drug as specified in the washout procedures (Inclusion Criterion 7, Section 5.2.1). For all other bDMARDs, contact the Therapeutic Area Medical Director for the washout period required prior to the first dose of study drug.

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

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

### **Immunosuppressants**

Subjects must have discontinued any immunosuppressant prior to the first dose of study drug as specified in the washout procedures (Inclusion Criterion 8, Section 5.2.1).

Examples of immunosuppressant therapies include but not limited to the following:

- Prograf® (tacrolimus)
- Imuran® (azathioprine)

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- Neoral® (cyclosporine)
- Bredinin® (mizolabine)

### **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**

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

### **Opiates**

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

- oxycodone

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

### **Investigational Drugs**

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

### **Vaccines**

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) 8 weeks before the first dose of study drug with appropriate precautions. Live vaccinations are prohibited during the study participation including at least 30 days 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);
- Herpes zoster;
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;

- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid.

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

If the nasal influenza vaccine is administered, the vaccine must be administered at least 8 weeks prior to first dose of study drug.

## **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 month are of childbearing potential and FSH is therefore not required but contraception is required.
- Female subjects who are surgical sterile (defined above) are not of childbearing potential and therefore no FSH testing or contraception is required.

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

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal\*, transdermal\*, injectable\*) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable\*, implantable\*) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal ligation.

- Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the only sexual partner.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

If required per local guidelines, 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 and complete documentation is available, contraception 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 exposure to the investigational therapy with upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant csDMARD and that duration of contraception after discontinuation of the csDMARD should be based on the local label.

### **Contraception Recommendation for Males**

For a male subject who has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

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

- Condom use, including also male subjects who have had a vasectomy less than 6 months earlier, and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

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

It is important to note that contraception and sperm recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study.

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

**5.3 Efficacy Pharmacokinetic, Pharmacodynamic, Exploratory Research and Validation Studies, and Safety Assessments/Variables****5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart**

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

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

Activity	Screening		BL	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 or PD <sup>a</sup>	30-Day F/U Visit <sup>c</sup>
	D-35 to D-1	D1 <sup>b</sup>	D8	D15	D29	D57	D85		
Informed consent <sup>d</sup>	X								
Inclusion/exclusion criteria	X	X							
Medical/surgical history <sup>e</sup>	X	X							
Alcohol and nicotine use	X								
Adverse event assessment <sup>f</sup>	X <sup>f</sup>	X							
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X
Patient questionnaires <sup>g</sup>									
PtGA									
Pain (VAS)									
HAQ-DI									
Morning Stiffness (severity and duration) <sup>g</sup>									
Patient questionnaires <sup>g</sup>									
EQ-5D-5L									
SF-36									
FACIT-F									
RA-WIS									
Latent TB risk factor assessment <sup>h</sup>		X							
Central lab QuantiFERON-TB Gold test <sup>h</sup> (or local PPD skin test)	X								
Chest x-ray <sup>i</sup>	X								
12-lead ECG <sup>j</sup>	X								

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

Activity	Screening		BL	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 or PD <sup>a</sup>	30-Day F/U Visit <sup>c</sup>
	D-35 to D-1	D1 <sup>b</sup>							
Height (screening only) and weight	X	X		X	X	X	X	X	X
Vital signs <sup>k</sup>	X	X	X	X	X	X	X	X	X
Physical exam <sup>l</sup>	X	X	X					X	
Physician's Global Assessment (PhGA)			X	X	X	X	X	X	
TJC68/SJC66		X	X	X	X	X	X	X	
Serum pregnancy test at central lab <sup>m</sup>	X								
Local urine pregnancy test <sup>n</sup>			X		X	X	X	X	X
Central lab tests		X	X	X	X	X	X	X	X
hsCRP <sup>o</sup>					X	X	X	X	X
Blood chemistry <sup>p</sup>									
Hematology (CBC)									
Urinalysis <sup>q</sup>									
ESR (local lab)	X	X	X	X	X	X	X	X	
Other central lab tests									
Rheumatoid factor									
Anti-CCP autoantibodies									
HBV/HCV screening <sup>r</sup>									
beta-D-glucan									
GFR by simplified 4-variable MDRD formula									
HIV <sup>s</sup>			X						
VZV skin test <sup>t</sup> and VZV specific IgG <sup>t</sup>		X							

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

Activity	Screening		BL	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12 or PD <sup>a</sup>	30-Day F/U Visit <sup>c</sup>
	D-35 to D-1	D1 <sup>b</sup>	D8	D15	D29	D57	D85		
IgG and IgM (central lab)	X						X		
Blood samples for upadacitinib PK assay		X <sup>u</sup>		X <sup>w</sup>		X <sup>w</sup>		X <sup>w</sup>	
Blood samples for intensive pharmacokinetic assessment <sup>v</sup>		X	X	X	X	X	X	X	
In vivo pharmacodynamic biomarkers	X						X	X <sup>x</sup>	X
Blood samples for exploratory research and validation studies (optional – see Table 3) <sup>y</sup>	X		X	X	X	X	X	X	
Randomization/Treatment group assignment	X								
Dispense study drug and subject dosing diary	X					X	X	X <sup>z</sup>	
Review and retain a copy of 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; GFR = Estimated glomerular filtration rate; 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; MDRD = Modification of Diet in Renal Disease; PD = Premature Discontinuation; PtGAs = Physician's Global Disease Activity; PK = pharmacokinetics; PPD = purified protein derivative; TJC = Patient's Global Assessment of Disease Activity; SAE = serious adverse event; SJIC = Swollen Joint Count; TB = tuberculosis; SF-36 = 36-Item Short Form Health Survey; VAS = visual analog scale; VZV = varicella-zoster virus; Wk = Week

- If a subject prematurely discontinues study drug treatment and study participation, 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.
- 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.

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

- 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 or for those subjects who prematurely discontinued study drug and study participation. A 30-day follow-up phone call may be allowed for subjects who have already completed PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.
- d. Obtain prior to performing any study related procedures.
- e. Note herpes zoster and hepatitis B vaccination status in medical history.
- f. Collect serious adverse events and protocol-related non-SAE 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. The Latent TB risk factor assessment and TB Testing will be performed in case of Premature Discontinuation visit but not at Week 12.
  - 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). Obtain chest x-ray at PD for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline.
  - 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. For subjects who do not enter Period 2 or prematurely discontinue from the study, an ECG will be performed. Refer to Section 5.3.1.1 12-Lead ECG for additional details.
  - k. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.
  - l. A full physical exam is required at the visits indicated. A symptom-directed physical exam may be performed when necessary.
  - m. For all 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). If still borderline  $\geq 3$  days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.
  - n. For all women of child bearing potential, collect urine for pregnancy test at Baseline and all subsequent visits except Week 1. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details. If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation is available, urine pregnancy test is no longer required.

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

- o. Central lab hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject for all visits except Screening. Investigator should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigator should also refrain from locally testing procalcitonin except for safety evaluations of signs and symptoms of infection management and adverse events. Results of hsCRP may unblind the treatment assignment and results of tests such as hsCRP, serum amyloid A and procalcitonin 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. Therefore, any local testing of hsCRP or CRP is strongly discouraged. It should also be noted that during Period 1 any hsCRP or CRP, serial SAA, or serial procalcitonin local tests reported to the Investigator will be recorded as protocol deviations.
- p. Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- q. A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.
- r. In HBs Ab positive (+) subjects and/or HBC Ab positive (+) subjects, HBV-DNA PCR test should be performed every 12 weeks (Week 12 and every 12 weeks thereafter). The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-DNA is observed. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+) and HBC Ab negative (-). Refer to Section 5.3.1.1 Study Procedures Hepatitis Screen for additional details.
- s. Subjects will be tested for antibodies to HIV at Screening, and it should be documented that the test has been performed. This testing is to be done centrally or at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.
- t. VZV skin test will be performed locally at Screening. VZV specific IgG should be measured centrally at Screening. If a subject had a VZV skin test within 90 days prior to Screening and source documentation is available, the test does not need to be repeated. Alternative methods other than VZV skin test are also acceptable to assess the cell-mediated immune status to VZV (e.g., IgRA). In case of shortage or inability to supply the test to assess the cell-mediated immune status to VZV, only IgG-class antibodies specific to VZV will be tested at Screening.
- u. At Week 1 and 2 visits, if possible, 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. Subjects who participate in the intensive pharmacokinetic assessment will be asked to fast for a minimum of 8 hours prior to the study visit selected for the intensive PK assessment (any single study visit, including unscheduled visits occurring after Week 1, during Period 1 or Period 2 excluding Baseline and Premature Discontinuation visit) and not to take the drug dose on the day of intensive PK assessment before coming for the visit. Subjects will be dosed during the visit and will continue fasting for 4 hours after dosing. No food or drinks will be allowed during fasting except water to quench thirst. Blood samples will be collected during the study visit selected for the intensive PK assessment prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose.
- w. PK samples should be collected at any time during the visit. Subject should follow the regular dosing schedule.

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

- x. In vivo pharmacodynamic biomarkers sample will be collected in case of Premature Discontinuation visit but not at Week 12.
- y. Samples only collected if subject provides written consent.
- z. For subjects entering Period 2.

**Note:** Visit window is  $\pm 3$  days for the study. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

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

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 12/PD
	D -35 to D -1	D1 <sup>a</sup>	D15	D29	D57	D85
Pharmacogenetic samples <sup>ab</sup>	--	X	--	--	--	--
Epigenetic samples <sup>b</sup>	--	X	X	X	--	X
Transcriptomic and epigenetic samples <sup>b</sup>	--	X	X	X	--	X
Plasma samples for proteomic and targeted protein investigations <sup>b</sup>	--	X	X	X	--	X
Serum samples for proteomic and targeted protein investigations <sup>b</sup>	--	X	X	X	--	X

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

- a. The sample is preferred to be collected at BL, but can be drawn at any time during the subject's participation.
- b. Based on the value of the different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches.

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

**Table 4.** Studies Activities (Period 2)

Activity	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks Until Study Completion <sup>a</sup>	Every 24 Weeks Until Study Completion <sup>a</sup>	Every 48 Weeks Until Study Completion <sup>a</sup>	Final/ PD Visit	30-Day F/U Visit <sup>b</sup>
Adverse event assessment	X	X	X	X	X		X			X	X
Concomitant therapy	X	X	X <sup>c</sup>	X	X		X			X	X
Patient questionnaires <sup>d</sup>	X	X	X	X	X		X			X	X
PtGA											
Pain (VAS)											
HAQ-DI											
Morning Stiffness (severity and duration) <sup>d</sup>											
Patient questionnaires <sup>d</sup>											
EQ-5D-5L											
SF-36											
FACT-T-F											
RA-WIS											
Latent TB risk assessment form											
Central lab QuantIFERON-TB Gold test <sup>e</sup> (and/or local PPD skin test)							X <sup>e</sup>		X <sup>c</sup>	X <sup>c</sup>	
Chest x-ray <sup>f</sup>							X <sup>f</sup>		X <sup>f</sup>		
12-lead ECG <sup>g</sup>							X		X		
Vital signs and body weight <sup>h</sup>	X	X	X	X	X		X		X	X	X
Physical exam <sup>i</sup>											
Physician Global Assessment (PhGA)	X	X	X	X	X		X		X		
TJC68/SJC66	X	X	X	X	X		X		X		
20% joint assessment (TJC and SJC) <sup>j</sup>							X	X	X		

**Table 4. Studies Activities (Period 2) (Continued)**

Activity	Wk 16		Wk 20		Wk 24		Wk 36		Wk 48		Monthly		Every 12 Weeks Until Study Completion <sup>a</sup>	Every 24 Weeks Until Study Completion <sup>a</sup>	Every 48 Weeks Until Study Completion <sup>a</sup>	Final/ PD Visit	30-Day F/U Visit <sup>b</sup>	
	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Wk 36	Wk 48	Monthly	Wk 48	Monthly	Wk 36						
CDAI IRT calculation <sup>k</sup>							X											
Local urine pregnancy test <sup>l</sup>			X	X	X	X	X	X	X	X	X				X	X		
In-home urine pregnancy test <sup>m</sup>									X									
Central lab tests																		
hsCRP <sup>n</sup>																		
Blood chemistry <sup>o</sup>																		
Hematology (CBC)																		
Urinalysis <sup>p</sup>																		
ESR (local lab)			X	X	X	X	X	X	X	X	X					X	X	
HBV screening <sup>q</sup>							X	X	X	X	X							
Blood samples for intensive pharmacokinetic assessment <sup>r</sup>			X	X	X	X	X	X	X	X	X							
In vivo pharmacodynamic biomarkers							X											
Dispense study drug and subject dosing diary			X	X	X	X	X	X	X	X	X							
Review and retain a copy subject dosing diary and perform drug reconciliation			X	X	X	X	X	X	X	X	X				X			

BL = Baseline Visit; CBC = complete blood count; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; ECG = electrocardiogram; F/U = Follow-up; HAQ-DI = Health Assessment Questionnaire – Disability Index; hsCRP = high-sensitivity C-reactive protein; NRS = numerical rating scale; PD = Premature Discontinuation; PhGA = Physician's Global Disease Activity; PPD = purified protein derivative; PGA = 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.

**Table 4. Studies Activities (Period 2) (Continued)**

- b. This visit is 30 days after last dose of study drug for those subjects who complete Period 2 or for those subjects who prematurely discontinued study drug and study participation. A 30-day follow-up phone call may be allowed for subjects who have already completed PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.
- c. At Week 24 (after Week 24 assessments have been performed), if a subject fails to meet LDA criterion (LDA defined as CDAI  $\leq$  10) investigator should adjust the subject's background RA therapies. Initiation of or change in corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses of csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 3) is allowed as per local label.
- 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 and at PD in subjects with previous negative Quantiferon and/or PPD tests. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines. Refer to Section 5.3.1.1 TB Testing/TB prophylaxis for additional details.
- f. Starting at Week 48, obtain chest x-ray every 48 weeks for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive QuantIFERON-TB Gold test (and/or PPD skin test) after baseline.
- g. Starting at Week 48, ECGs will be performed every 48 weeks and for subjects who prematurely discontinue from the study. 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 24 and thereafter, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits should be discontinued from the study.
- k. CDAI calculation requires input of SJC28 + TJC28 + PtGA + PhGA into IRT system. At Week 24, investigator should optimize background RA therapies in subjects who failed to achieve CDAI  $\leq$  10.
  - l. For women of childbearing potential, a urine pregnancy test will be performed at all visits and monthly at home between scheduled study visits. Pregnant subjects must discontinue from the study. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details. If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation is available, urine pregnancy test is no longer required.
  - m. Starting at Week 24, for women of childbearing potential, in-home urine pregnancy tests will be performed monthly. 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. If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation is available, urine pregnancy test is no longer required.

**Table 4. Studies Activities (Period 2) (Continued)**

n. Central lab hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject. Treatment assignment may be unblinded to Sponsor only when the last subject completes Period 1 (Week 12 visit) for the Week 12 primary analysis. Study sites and subjects will remain blinded throughout Periods 1 and 2. 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. Therefore, any local testing of hsCRP or CRP is strongly discouraged.

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.

q. In HBs Ab positive (+) subjects and/or HBC Ab positive (+) subjects, HBV-DNA PCR test should be performed in every 12 weeks. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+) and HBC Ab negative (-). Refer to Section 5.3.1.1 Study Procedures Hepatitis Screen for additional details.

r. The intensive pharmacokinetic assessment can be performed at any single visit, including unscheduled visits occurring after Week 1, during Period 1 or Period 2 excluding Baseline and Premature Discontinuation visit. Subjects who participate in the intensive pharmacokinetic assessment will be asked to fast for a minimum of 8 hours prior to the study visit selected for the intensive pharmacokinetic assessment and not to take the drug dose on the day of intensive pharmacokinetic assessment before coming for the visit. Subjects will be dosed during the visit and will continue fasting for 4 hours after dosing. No food or drinks will be allowed during fasting except water to quench thirst. Blood samples will be collected during the study visit selected for the intensive pharmacokinetic assessment prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose. Subjects who complete the intensive pharmacokinetic assessment during Period 1 cannot participate again during Period 2.

**Note:** Visit window is  $\pm$  7 days for the study. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

### **5.3.1.1                    Study Procedures**

The study procedures outlined in [Table 2](#) and [Table 4](#) are discussed in detail in this section, with the exception of in vivo pharmacodynamic biomarkers (discussed in Section [5.3.1.2.1](#)), exploratory research and validation studies (discussed in Section [5.3.1.2.2](#)), drug concentration measurements (discussed in Section [5.3.2](#)), the collection of prior and concomitant medication information (discussed in Section [5.2.3](#)), and the collection of AE information (discussed in Section [6.0](#)). All study data will be recorded in source documents and on the appropriate eCRFs.

#### **Informed Consent**

At the Screening visit, the subject will sign and date a study specific, IEC/IRB approved, informed consent form for the study (i.e., includes both Periods 1 and 2) before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Separate written consent will be required for each subject in order to participate in the optional exploratory research and validation studies. Subjects can withdraw informed consent at any time.

Details regarding how informed consent will be obtained and documented are provided in Section [9.3](#).

#### **Inclusion/Exclusion Criteria**

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

#### **Medical and Surgical History**

A complete non-RA-related medical and surgical history, including history of alcohol and nicotine use, will be taken from each subject during the Screening Visit. Additionally, a list of each subject's specific RA-related medical and surgical history will be recorded at Screening. History of herpes zoster, herpes zoster vaccination, and hepatitis B vaccination status will be recorded as part of the medical history. An updated medical

history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment.

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

### **Patient Questionnaires**

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

#### *Period 1 and Period 2*

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

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

The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

### **TB Testing/TB Prophylaxis**

#### *Period 1*

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form ([Appendix E](#)) and tested for TB infection by an Interferon-Gamma Release Assay (IGRA; QuantiFERON<sup>®</sup>-TB Gold) test. The PPD Skin Test should be utilized only when a QuantiFERON<sup>®</sup>-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines). The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF. The assessment for TB risk and TB test will be repeated at Premature Discontinuation visit.

Preferred Method:

- QuantiFERON<sup>®</sup>-TB Gold Test will be analyzed by the central laboratory (QuantiFERON<sup>®</sup> test is preferred over PPD skin).
- If the QuantiFERON<sup>®</sup>-TB Gold Test is NOT possible (or if both the QuantiFERON<sup>®</sup>-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  $\geq 5$  mm for RA subjects is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had an ulcerating reaction to the TB Skin Test

in the past should not be re-exposed and should not be tested by a PPD skin test.

If a subject had a negative QuantiFERON®-TB Gold (and/or PPD) test (or IGRA equivalent such as T-SPOT TB test) within 90 days prior to Screening and source documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TA MD. The results of the TB test(s) will be retained at the site as the original source documentation.

In the event both a PPD test and a QuantiFERON®-TB Gold test are performed, the result of the QuantiFERON®-TB Gold test will supersede the result of the PPD test unless otherwise required by local guidelines. If the QuantiFERON®-TB Gold test is indeterminate, the site should repeat the test with another blood sample. If the second QuantiFERON®-TB Gold test is also indeterminate, the subject is considered to be positive. At a site with capacity to perform both tests, if a PPD is placed as the only form of TB test at Screening, then the TB test to be used for the remainder of the study for that subject is the PPD. Similarly, if a subject enters the study with a QuantiFERON®-TB Gold test alone or other IGRA (negative result), then the subject should have their annual TB test performed with the QuantiFERON®-TB Gold test.

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

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

At Screening, if the subject has evidence of latent TB infection (QuantiFERON®-TB Gold test and/or the PPD test positive) and has a CXR not suggestive of active TB, prophylactic

treatment must be initiated at least 3 weeks prior to administration of study drug per local guideline in Japan. 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 are not allowed for TB prophylaxis.**

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy within 1 year prior to first study drug administration will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

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

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

*Period 2*

Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD are not required to repeat either TB test during the study and should be considered positive. The TB risk assessment form will be completed annually for all subjects, regardless of TB test results.

For subjects with a negative QuantiFERON<sup>®</sup>-TB Gold (and/or PPD) test at Screening, a QuantiFERON<sup>®</sup>-TB Gold (and/or PPD) re-test will be performed (or both if required by local guidelines) annually and at PD.

If one of the annual tests has a positive test result (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB.

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.

Expert consultation for the evaluation/management of TB may be considered per Investigator's discretion.

Any positive TB screen after the patient has started the study, should be reported as an adverse event (AE) of latent TB or active TB (as applicable).

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

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

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

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

### **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 TB risk factors as identified by the TB risk assessment form ([Appendix E](#)), or for subjects living in areas endemic for TB or for subjects with newly positive PPD and/or QuantiFERON<sup>®</sup>-TB Gold test.

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

A radiologist, internist or pulmonologist must perform an assessment of the CXR. The Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator should contact the AbbVie TA MD before enrolling the subject.

### **12-Lead ECG**

A resting 12-lead ECG will be performed at the designated study visits as specified in [Table 2](#) and [Table 4](#). A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. ECG with QT interval corrected for heart rate using Friedericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed. A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. In case of QTcF prolongation, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, any clinically significant findings will be documented in

the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible site monitor and kept with subject's source documents onsite.

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

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

### **Height and Weight**

Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits except Week 1 as specified in [Table 2](#) and [Table 4](#). All measurements will be recorded in metric units where applicable.

### **Vital Signs**

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at visits specified in [Table 2](#) and [Table 4](#). Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

### **Physical Examination**

A complete physical examination will be performed at the designated study visits as specified in [Table 2](#) and [Table 4](#). The physical examination at the Baseline Visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted by the Investigator at Baseline prior to the first dose of study drug will be recorded in the subject's medical history; abnormalities noted after the first dose of study drug will be evaluated and documented by the Investigator as to whether or not the

abnormality is an AE (see Section 6.1.1.1 for AE definition). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

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

### **Physician's Global Assessment of Disease Activity VAS**

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

### **TJC and SJC Assessment**

#### *TJC Assessment*

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

#### *SJC Assessment*

An assessment of 66 joints ([Appendix D](#)) will be done by directed physical examination at visits specified in [Table 2](#) and [Table 4](#). The joints to be examined for swelling are the same as those examined for tenderness, except the hip joints are excluded. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9") or no assessment ("NA").

Any injected joints will be considered as "not assessed" ("NA") for 3 months from the time of the intra-articular injection.

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

In order to minimize variability, the same independent joint assessor should evaluate the subject at each visit for the duration of the trial as much as possible. A back-up independent joint assessor should be identified. The independent joint 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.

### **CDAI**

The CDAI calculation is required to determine if a subject fails to achieve low disease activity at the Week 24 visit. An Interactive Response Technology (IRT) will calculate CDAI with input from site personnel on joint counts and the subject's and physician's Global Assessment of RA Disease Activity score. A worksheet will be provided to capture the components required for IRT entry to obtain the CDAI calculation.

The calculation used to determine CDAI score at Week 24 is as follows:

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

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

### **Pregnancy Test**

A serum pregnancy test will be performed for all women of childbearing potential at the Screening Visit. Women of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing. 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  $\geq 3$  days later to determine eligibility. If the repeat serum pregnancy test is:

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

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

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required.
- If a urine pregnancy test post-baseline is positive, study drug needs to be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may be resumed. 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 ( $\geq 3$  days later) to document continued lack of a positive result.

In Period 2 starting at Week 24, for women of childbearing potential, a urine pregnancy test will be performed at all visits and monthly at home between scheduled study visits. The results of the monthly at home tests will be communicated to the site. If a urine

pregnancy test is positive, the subject must stop dosing, come in to the clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory.

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

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

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

### **Clinical Laboratory Tests**

Samples will be obtained for the clinical laboratory tests listed in [Table 5](#). Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per Investigator's discretion. A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. In cases where laboratory tests are performed locally for specific study purposes, certifications and laboratory reference ranges will be collected for the tests which are performed. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

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

Blood samples will be obtained for the laboratory tests at visits specified in [Table 2](#) and [Table 4](#). Blood draws should be performed only after all clinical assessments and questionnaires (HAQ-DI, Patient's Assessment of Pain, etc.) and vital sign determinations are obtained.

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

Urine samples will be obtained for urinalysis testing at visits specified in [Table 2](#) and [Table 4](#). The central laboratory will be responsible for performing a macroscopic urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

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

- The Investigator will repeat the test to verify the out-of-range value at Investigator's discretion.
- 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 5. Clinical Laboratory Tests**

Hematology (Central Lab)	Clinical Chemistry <sup>a</sup> (Central Lab)	Urinalysis <sup>b</sup> (Central Lab)	Other Laboratory Tests
Hematocrit	BUN	Specific gravity	Central Lab Tests:
Hemoglobin	Creatinine	Ketones	Serum pregnancy
RBC count	Total bilirubin	pH	(bHCG) test <sup>d</sup>
WBC count	INR <sup>c</sup>	Protein	GFR by simplified
Neutrophils	ALT	Blood	4-variable MDRD
Bands	AST	Glucose	formula <sup>f</sup>
Lymphocytes	Alkaline phosphatase	Urobilinogen	HBs Ag <sup>f</sup>
Monocytes	CPK	Bilirubin	HBs Ab <sup>f</sup>
Basophils	Sodium	Leukocytes	HBc Ab <sup>f</sup>
Eosinophils	Potassium	Nitrites	HBV DNA PCR reflex
Platelet count	Chloride	Microscopic examination, if needed	only <sup>e,f</sup>
	Bicarbonate		HCV Ab <sup>f</sup>
	Calcium		HCV RNA reflex only <sup>f</sup>
	Inorganic phosphate		QuantiFERON-TB
	Uric acid		Gold <sup>g</sup>
	Cholesterol		Rheumatoid Factor <sup>f</sup>
	LDL-C		Anti-CCP
	HDL-C		autoantibodies <sup>f</sup>
	Total protein		hs-CRP <sup>h</sup>
	Glucose		IgG and IgM
	Triglycerides		VZV specific IgG <sup>f</sup>
	Albumin		HIV <sup>i</sup>
			beta-D-glucan <sup>f</sup>
			MRB Panel <sup>j</sup>
			FSH <sup>f,k</sup>
			Local Lab Tests:
			Urine pregnancy test <sup>l</sup>
			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; GFR = Estimated glomerular filtration rate; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; MDRD = Modification of Diet in Renal Disease; PCR = polymerase chain reaction; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell

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**Table 5. Clinical Laboratory Tests (Continued)**

- a. Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- b. A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.
- c. INR will be measured with a separate blood sample if ALT and/or AST  $> 3 \times$  ULN.
- d. 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.
- e. In case of HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV-DNA PCR test should be performed every 12 weeks. HBV-DNA PCR testing every 12 weeks is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+) and HBc Ab negative (-).  
HBV DNA testing is also required for subjects who meet specific toxicity management criteria (See ALT/AST toxicity management criteria in [Table 7](#)).
- f. At Screening only.
- g. At Screening, annually and at PD, if PPD not performed.
- h. 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 be blunted in subjects taking a JAK inhibitor, thereby limiting its clinical utility in the setting of a possible safety assessment or adverse event management. 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.
- i. Subjects will be tested for antibodies to HIV at Screening, and it should be documented that the test has been performed. This testing is to be done centrally or at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.
- j. If needed to assess B cell counts in subjects who have discontinued rituximab, see Inclusion criteria 7.
- k. For more details, please refer to Section 5.2.4 (Contraception Recommendations).
- l. A urine pregnancy test will be performed for all women of childbearing potential at the Baseline Visit prior to the first dose of study drug and all subsequent visits except Week 1. In Period 2, for women of childbearing potential, a urine pregnancy test will be performed at all visits, including the 30 days follow-up visit, and starting at Week 24 a urine pregnancy test will be performed monthly at home between scheduled study visits. 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 started or resumed. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required ( $\geq 3$  days later) to document continued lack of a positive result. 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.

## **Hepatitis Screen**

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

### *Hepatitis B:*

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

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

A positive result for HBs Ag will be exclusionary.

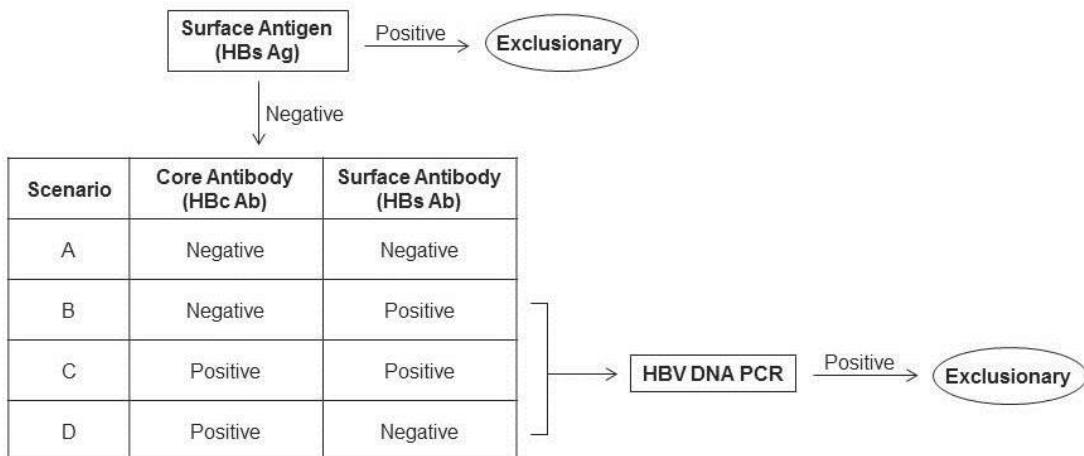
A negative result for HBs Ag will be tested (automatic reflex testing) for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

- A negative test result for HBc Ab and HBs Ab does not require HBV DNA PCR qualitative testing and the subject may be enrolled ([Figure 3](#), Scenario A). 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.
- A positive test result for HBc Ab or HBs Ab requires HBV DNA PCR testing (automatic reflex testing) ([Figure 3](#), Scenarios B, 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.
  - For subjects with HBs Ab positive (+) and/or HBc Ab positive (+) and negative HBV DNA at screening, HBV DNA PCR test should be performed every 12 weeks. HBV-DNA PCR testing every 12 weeks is not necessary in case of patients with history of HBV vaccine and HBs Ab positive (+) and HBc Ab negative (-).
  - Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop a positive result for HBV DNA PCR

testing during the study accompanied by the following should be referred to a hepatologist within 1 week for consultation and recommendation regarding subsequent treatment, and study drug interruption should be considered per local guidelines:

- an ALT  $> 5 \times$  ULN OR
- ALT or AST  $> 3 \times$  ULN and either a total bilirubin  $> 2 \times$  ULN or INR  $> 1.5$  OR
- ALT or AST  $> 3 \times$  ULN along with clinical signs of possible hepatitis.

**Figure 3. Criteria for HBV DNA PCR Qualitative Testing**



### *Hepatitis C:*

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

### **HIV**

Subjects with a known history of HIV infection are excluded from study participation. Subjects will be tested for antibodies to HIV at Screening. This testing is to be done

centrally or at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

### **VZV**

Tests for varicella-zoster virus (VZV) will be performed at Screening to evaluate immunity of a subject to VZV for better understanding of the safety profile of upadacitinib.

To assess the cell-mediated immune status to VZV, a skin test using the VZV antigen will be performed. VZV antigen is injected intradermally into the forearm of each subject, and the longest diameters of erythema and edema will be measured in millimeters (mm) between 24 (recommended) and 48 hours after the injection and recorded on the appropriate eCRF page along with date and time of injection and measurement. The absence of erythema or edema will be recorded as "0 mm." If a subject had a VZV skin test within 90 days prior to Screening and source documentation is available, the test does not need to be repeated.

Blood samples will be used for measuring IgG-class antibodies specific to VZV to estimate the prior exposure to VZV of the subject.

Alternative methods other than VZV skin test are also acceptable to assess the cell-mediated immune status to VZV (e.g., IGRA).

In case of shortage or inability to supply the tests to assess the cell-mediated immune status to VZV, only IgG-class antibodies specific to VZV will be tested at Screening.

### **Beta-D-glucan**

All subjects will be tested for beta-D glucan at Screening. A positive result or two consecutive indeterminate results for beta-D-glucan will be exclusionary.

### **Randomization/Treatment Group Assignment**

All Screening laboratory results must be reviewed, signed and dated by the 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 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 3:3:3:1:1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: upadacitinib 7.5 mg QD (N = 48) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 2: upadacitinib 15 mg QD (N = 48) (Period 1) → ABT-494 upadacitinib 15 mg QD (Period 2)
- Group 3: upadacitinib 30 mg QD (N = 48) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → upadacitinib 30 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/no).

See Section 5.5.3 for details.

### **Study Drug Dispensing, Dosing, and Compliance**

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Table 2 and Table 4. The first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed. Subjects will maintain a dosing diary for all study drug administered outside of the study visit (i.e., at home) to capture dosing dates and times. At visits specified in Table 2 and Table 4, the site personnel will review and

retain a copy of the dosing diary, returned study drug kits, and empty study drug packaging to verify compliance.

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

(Refer to Section [5.5](#) for additional information.)

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

##### **5.3.1.2.1      In Vivo Pharmacodynamic Biomarker Samples**

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

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

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on upadacitinib (or drugs of this class) or this disease and related conditions continues, but for no longer than 5 years after study completion, or per local requirement.

##### **5.3.1.2.2      Optional Samples for Exploratory Research and Validation Studies**

In Period 1, subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research/validation study.

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

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

Research on DNA and RNA exploratory research samples will be restricted to the subject's response to treatment in terms of pharmacokinetics, efficacy, tolerability, and safety.

AbbVie (or people or companies working with AbbVie) will store the exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on upadacitinib (or drugs of this class) or RA and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

### **DNA Samples for Pharmacogenetic or Epigenetic Analyses**

Optional whole blood samples for DNA isolation will be collected at the visits indicated in Table 3 from each subject who consents to provide samples for exploratory/validation research. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

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

### **RNA Samples for Transcriptomic and/or Epigenetic Analyses**

Optional whole blood samples for RNA isolation will be collected at the visits indicated in Table 3 from each subject who consents to provide samples for exploratory/validation research. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

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

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

Serum and plasma samples will be collected at the visits indicated in Table 3 from each subject who consents to provide samples for exploratory/validation research. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

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

#### **5.3.2 Drug Concentration Measurements**

##### **5.3.2.1 Collection of Samples for Analysis**

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

- At Weeks 1 and 2 prior to dosing in all subjects;
- At Weeks 4, 8, and 12/Premature Discontinuation at any time during the visit in all subjects.
- During one of the study visits, including unscheduled visits occurring after Week 1, in Period 1 or Period 2 excluding Baseline and Premature Discontinuation visit prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and

24 hours after dose in approximately 32 subjects who participate in the intensive pharmacokinetic study.

On Week 1 and Week 2 visit days, if possible, subjects should take the study drug dose at the clinic after collecting the pharmacokinetic (PK) blood sample, except if the subjects regularly take the study drug dose at night. Those subjects who regularly take the 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.

Subjects who participate in the intensive pharmacokinetic assessment (approximately 32 subjects) should be fasting for at least 8 hours prior to drug administration and will not take the study drug until after collection of the pre-dose blood sample during the study visit chosen for intensive PK assessment. Subjects will continue fasting for 4 hours after dosing. No food or drinks will be allowed during fasting except water to quench thirst. Subjects will be confined to the study site and supervised for approximately 2 days if necessary. The intensive PK assessment can be done at any single visit, including unscheduled visits occurring after Week 1, during Period 1 or Period 2 excluding Baseline and Premature Discontinuation visit. Confinement will begin on the day before intensive PK visit and end after the collection of the 24-hour blood sample the next day of intensive PK visit. Subjects cannot complete the intensive pharmacokinetic assessment more than once during the study.

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 for all subjects at all visits.

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

**5.3.2.2 Measurement Methods**

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

**5.3.3 Efficacy Variables****5.3.3.1 Period 1 Variables****5.3.3.1.1 Primary Variables**

The primary endpoint in Period 1 is the proportion of subjects achieving ACR20 response at Week 12.

ACR20 response rate will be determined based on 20% or greater improvement in TJC and SJC and  $\geq 3$  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.

**5.3.3.1.2 Key Secondary Variables**

Key secondary endpoints at Week 12 (if not otherwise indicated) are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. ACR50 response rate;
4. ACR70 response rate;
5. Change from baseline in SF-36 Physical Component Score (PCS);
6. Proportion of subjects achieving Low Disease Activity (LDA) based on DAS28 (CRP);
7. Proportion of subjects achieving Clinical Remission (CR) based on DAS28 (CRP);

8. ACR20 response rate at Week 1;
9. Change from baseline in FACIT-F;
10. Change from baseline in RA-WIS;
11. Change from baseline in morning stiffness (severity).

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 12.

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

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

ACR50/70 response rates will be determined based on 50%/70% or greater improvement in TJC and SJC and  $\geq 3$  of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQ-DI, or hsCRP.

### **5.3.3.1.3 Additional Variables**

Additional endpoints at all visits are:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in morning stiffness (severity and duration);

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- 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);

	<b>DAS28 (CRP) and DAS28 (ESR)</b>	<b>SDAI</b>	<b>CDAI</b>
LDA	$\leq 3.2$	$\leq 11.0$	$\leq 10$
CR	$< 2.6$	$\leq 3.3$	$\leq 2.8$

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

### **5.3.3.2            Period 2 Variables**

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 16, 20, 24, 36, 48, and every 12 weeks thereafter until completion of the study:

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

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

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

#### **5.3.4 Safety Variables**

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

#### **5.3.5 Pharmacokinetic Variables**

Plasma upadacitinib concentrations will be obtained at the times indicated in [Table 2](#). A non-linear mixed-effects modeling approach will be used to estimate the population central value and the empirical Bayesian estimates of the individual values of upadacitinib oral clearance (CL/F) and volume of distribution (V/F).

For the subjects who participate in the intensive pharmacokinetic assessment, the values for the maximum observed concentration ( $C_{max}$ ), the time to  $C_{max}$  (peak time,  $T_{max}$ ), the area under the plasma concentration-time curve (AUC), the apparent oral clearance (CL/F), the plasma concentration at the end of dosing interval ( $C_{trough}$ ), and the minimum plasma concentration over a 24-hour period at steady state ( $C_{min}$ ) will be determined at Week 1 using noncompartmental methods.

Additional parameters may be estimated if useful in the interpretation of the data.

**5.3.6      In Vivo Pharmacodynamic Biomarker Samples and Exploratory Research Variables and Validation Studies****5.3.6.1      In Vivo Pharmacodynamic Biomarker Samples**

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

**5.3.6.2      Exploratory Research Variables and Validation Studies**

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

Genetic (DNA and RNA) exploratory research will be restricted to the subject's response to treatment in terms of pharmacokinetics, efficacy, tolerability and safety.

The serum and plasma biomarker samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies.

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. The results from genetic and biomarker analyses are exploratory in nature and may not be included with the clinical study report (CSR).

**5.4 Removal of Subjects from Therapy or Assessment****5.4.1 Discontinuation of Individual Subjects**

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

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

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

- Subject develops a gastrointestinal perforation.
- Starting at Week 24, at least 20% improvement in BOTH TJC and SJC compared to baseline is required to remain in the study. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) must be discontinued from the study.
- If a subject is unblinded in Period 1, as summarized in Section [5.5.5](#).

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. A 30-day follow-up visit/phone call may occur for subjects who prematurely discontinued from study drug and study participation to determine the status of any upadacitinib ongoing AEs/SAEs or the occurrence of any new AEs/SAEs (refer to Section [5.1](#) regarding Follow-Up Visit). Subjects who discontinue the study prematurely after randomization will not be replaced.

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

### **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.

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**5.4.2 Discontinuation of Entire Study**

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

**5.5 Treatments****5.5.1 Treatments Administered**

Study drug will be taken orally once daily, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day. The study drug can be taken with or without food. Subjects will continue their stable therapy of csDMARD. AbbVie will not supply csDMARD(s) (nor folic acid or equivalent, such as folinic acid, for subjects who are on MTX).

**5.5.2 Identity of Investigational Product**

The individual study drug information is presented in [Table 6](#).

**Table 6. Identity of Investigational Product**

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib	Oral	Tablet (extended-release)	7.5mg 15 mg 30 mg	[REDACTED]
Matching placebo	Oral	Tablet	NA	[REDACTED]

### **5.5.2.1 Packaging and Labeling**

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

### **5.5.2.2 Storage and Disposition of Study Drugs**

Upadacitinib must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

### **5.5.3 Method of Assigning Subjects to Treatment Groups**

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

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

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

Subjects will be randomized in a 3:3:3:1:1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: upadacitinib 7.5 mg QD (N = 48) (Period 1) → upadacitinib 7.5 mg QD (Period 2)

- Group 2: upadacitinib 15 mg QD (N = 48) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 3: upadacitinib 30 mg QD (N = 48) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → upadacitinib 30 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/no).

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

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

#### **5.5.4 Selection and Timing of Dose for Each Subject**

Subjects should take study drug as outlined in Section 5.5.1.

On dosing days that occur on study visit days, subjects should follow the regular dosing schedule (refer to Section 5.3.2.1 regarding Week 1 and Week 2 visits).

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

If a subject should forget to take their upadacitinib (or matching placebo) dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled

dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time. If the subject experiences a study drug interruption > 7 consecutive days during Weeks 1 through 24 or > 30 consecutive days after Week 24 (other than for reasons listed in Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from the study.

### **5.5.5                   Blinding**

#### **5.5.5.1               Blinding of Investigational Product**

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

In the event of a medical situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the Investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the Investigator. If the IRT system is unavailable, unblinding may occur by contacting EndPoint technical support via either phone (preferred) or email

[REDACTED]. For country-specific phone numbers, please see the following website: <http://www.endpointclinical.com/help-desk/>.

In the event that the blind is broken before notification to the AbbVie TA MD, AbbVie requests that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded

on the appropriate eCRF. If a subject is unblinded in Period 1, they will be discontinued from the study.

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

#### **5.5.5.2                   Blinding of Data for Data Monitoring Committee**

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

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

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

#### **5.5.6                   Treatment Compliance**

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

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

**5.5.7****Drug Accountability**

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

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

All empty/used study drug packaging will be inventoried by the site and verified by the site monitor. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary. Empty/used packaging will be retained (unless prohibited by local law) until the site monitor is on site to confirm the returned study drug. Site monitor(s) and site staff will complete study drug accountability via IRT, source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible. After drug accountability has been completed, unused study drug and used packaging (if necessary) will be returned to the AbbVie-designated destruction depot by the site monitor.

**5.6****Discussion and Justification of Study Design****5.6.1****Discussion of Study Design and Choice of Control Groups**

This study includes two periods.

Period 1 is a 12 week, randomized, double-blind, placebo-controlled period to confirm dose response in the efficacy of upadacitinib 7.5 mg QD and 15 mg QD and 30 mg QD, and to compare the safety and efficacy of upadacitinib versus placebo in subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 1 is designed to test superiority of

upadacitinib versus placebo for achieving the primary endpoint (ACR20) at Week 12, and other secondary efficacy parameters, all on a stable csDMARD therapy.

The purpose of Period 2 is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 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 7.5 mg QD, 15 mg QD and 30 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments. Preventing dose reduction or escalation of upadacitinib during Period 2 will allow better assessments of long-term safety and efficacy of upadacitinib 7.5 mg QD, 15 mg QD versus 30 mg QD.

### **5.6.2                   Appropriateness of Measurements**

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

### **5.6.3                   Suitability of Subject Population**

The intended study population is moderately to severely active RA patients who have had an inadequate response to prior csDMARD treatment. Key entry criteria are to enroll adult female and male subjects who are at least 18 years of age with a diagnosis of RA for  $\geq 3$  months who also fulfill the 2010 ACR/EULAR classification criteria for RA. Eligible study subjects must have  $\geq 6$  swollen joints (based on 66 joint counts) and  $\geq 6$  tender joints (based on 68 joint counts) at Screening and Baseline Visits, and hsCRP level ( $\geq 3$  mg/L) at Screening.

Subjects must have been on a stable dose of csDMARD therapy (restricted to MTX, sulfasalazine, leflunomide, bucillamine or iguratimod) for  $\geq 4$  weeks prior to the first dose of study drug.

#### **5.6.4 Selection of Doses in the Study**

Three doses of the once-daily formulation of upadacitinib will be evaluated: upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD. The dose selection in this study is based on extrapolation of pre-clinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the Phase 1 studies in healthy volunteers (single and multiple ascending dose Studies M13-401 and M13-845, respectively, and Asian Study M13-543) and Phase 2 studies in RA subjects (Studies M13-537 and M13-550). The doses selected for Study M14-663, upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD, dosed for approximately 3 years and half are expected to be efficacious with an acceptable safety profile.

The once-daily formulation (tablet) of 7.5 mg, 15 mg and 30 mg QD doses to be used in this study are expected to have comparable daily AUC and  $C_{trough}$  to the 3 mg BID, 6 mg BID and 12 mg BID immediate release doses (capsule) used in the global Phase 2 studies, respectively. 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 and the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section [6.1.7](#) regarding toxicity management]) and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during the study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

#### **6.1.1.2                    Serious Adverse Events**

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE.

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<b>Death of Subject</b>	An event that results in the death of a subject.
<b>Life-Threatening</b>	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.
<b>Hospitalization or Prolongation of Hospitalization</b>	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.
<b>Congenital Anomaly</b>	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
<b>Persistent or Significant Disability/Incapacity</b>	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).
<b>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome</b>	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

### **6.1.1.3 Adverse Events of Special Interest**

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

- Serious infections
- Opportunistic infections
- Herpes zoster
- Tuberculosis;
- Malignancy (all types);
- Gastrointestinal perforations;
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Lipid profile changes;
- Anemia;
- Neutropenia;
- Lymphopenia;
- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Elevated creatine phosphokinase (CPK);
- Embolic and thrombotic events (non-cardiac, non-CNS).

### **6.1.2 Adverse Event Severity**

The investigator will classify AEs according to the Rheumatology Common Toxicity Criteria v.2.0 ([Appendix N](#)).<sup>22</sup>

### **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:

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

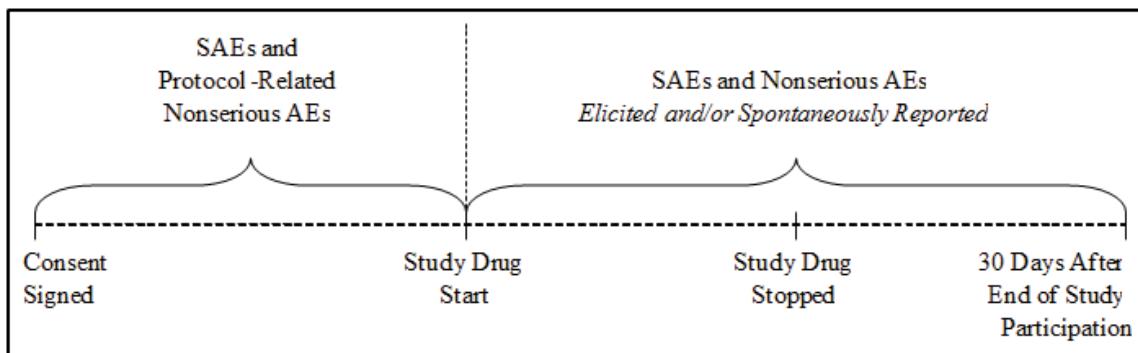
For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator 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**

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

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

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures (SAE Supplemental Procedure eCRF).

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

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

**6.1.5****Serious Adverse Event Reporting**

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

**Email:** [REDACTED]**FAX to:** [REDACTED]

For safety concerns, contact Medical Science Group at:

Medical Science Group  
3-5-27, Mita, Minato-ku, Tokyo, 108-6302

Office: [REDACTED]

Email: [REDACTED]

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

Primary Therapeutic Area Medical Director:

[REDACTED]  
AbbVie Deutschland GmbH & Co. KG  
Knollstrasse – [REDACTED]  
67061 Ludwigshafen  
Germany

Contact Information:

Office: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

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Secondary Contact (Regional Medical Monitor):

AbbVie GK  
3-5-27 Mita, Minato  
Tokyo, 108-6302  
Japan

Contact Information:

Office: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) 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 TA MD:

**Phone:** [REDACTED]

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

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

#### **6.1.6      Pregnancy**

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

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

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 and their partners should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration for female subjects and through 30 days after the last study drug administration for male subjects. Male subjects should refrain from donating sperm for up to 30 days post last dose of study drug. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

#### **6.1.7                   Toxicity Management**

The toxicity management of the AEs including AEs of special interest consists of safety monitoring (review of AEs on an ongoing basis, and periodical/ad hoc review of safety issues by a safety data monitoring committee), interruption of study drug dosing with appropriate clinical management if applicable, and discontinuation of the subjects from the study. The management of specific AEs and laboratory parameters is described below.

**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 the study.

**Serious Gastrointestinal Events:** Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued.

**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.

**Malignancy:** Subjects who develop malignancy other than NMSC or carcinoma in situ of the cervix must be discontinued. Information including histopathological results should be queried for the confirmation of the diagnosis.

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

**Management of Select Laboratory Abnormalities:** For any given laboratory abnormality, the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in [Table 7](#) and may require an appropriate supplemental eCRF to be completed. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a

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

**Table 7. Specific Toxicity Management Guidelines for Abnormal Laboratory Values**

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

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

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	<ul style="list-style-type: none"> <li>• Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 3 \times</math> ULN by repeat testing with new sample and either a total bilirubin <math>&gt; 2 \times</math> ULN or an international normalized ratio (INR) <math>&gt; 1.5</math>. <ul style="list-style-type: none"> <li>◦ INR will be measured with a separate blood sample every time subjects have ALT or AST <math>&gt; 3 \times</math> ULN by the central lab. A repeat test of INR is not needed for determination if above toxicity management criteria are met.</li> </ul> </li> <li>• Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 3 \times</math> 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 (<math>&gt; 5\%</math>).</li> <li>• Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 5 \times</math> ULN by repeat testing with new sample for more than 2 weeks.</li> <li>• Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 8 \times</math> ULN by repeat testing with new sample.</li> </ul> <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. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found.</p> <p>For any confirmed ALT or AST elevations <math>&gt; 3</math> ULN, complete supplemental hepatic eCRF.</p> <ul style="list-style-type: none"> <li>• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within 1 week: <ul style="list-style-type: none"> <li>◦ ALT <math>&gt; 5 \times</math> ULN OR</li> <li>◦ ALT or AST <math>&gt; 3 \times</math> ULN and either a total bilirubin <math>&gt; 2 \times</math> ULN or INR <math>&gt; 1.5</math> OR</li> <li>◦ ALT or AST <math>&gt; 3 \times</math> ULN along with clinical signs of possible hepatitis.</li> </ul> </li> </ul> <p>Subjects who develop a positive result for HBV DNA PCR testing should be referred to a hepatologist within 1 week for consultation and recommendation regarding subsequent treatment, and study drug interruption should be considered per local guidelines.</p>

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

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	<ul style="list-style-type: none"> <li>If serum creatine is <math>&gt; 1.5 \times</math> the baseline value and <math>&gt;</math> 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 <math>\leq 1.5 \times</math> baseline value and <math>\leq</math> ULN.</li> <li>If confirmed serum creatinine <math>\geq 2</math> mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value.</li> </ul> <p>For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.</p>
Creatine Phosphokinase	<ul style="list-style-type: none"> <li>If confirmed CPK value <math>\geq 4 \times</math> ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subject may continue study drug at the investigator's discretion.</li> <li>If CPK <math>\geq 4 \times</math> ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD.</li> </ul> <p>For the above CPK elevation scenarios, complete supplemental CPK eCRF.</p>

For allowed study drug interruption, the following rules apply:

### Period 1

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

### Period 2

- Allow study drug interruption up to 7 consecutive days for AEs and emergency surgery during Week 12 to Week 24 in Period 2 and after Week 24 and thereafter, up to 30 consecutive days of study drug interruption is allowed.

- If the subject undergoes elective surgery, the study drug should be interrupted 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

### **6.1.8                   Data Monitoring Committee**

An external DMC will review unblinded safety data. See Section [5.5.5.2](#).

### **6.1.9                   Cardiovascular Adjudication Committee**

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

## **6.2                      Product Complaint**

### **6.2.1                   Definition**

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

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

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

### **6.2.2 Reporting**

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

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

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

## **7.0 Protocol Deviations**

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

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Primary Contact:



AbbVie Srl  
Viale dell'Arte, 25  
00144 Roma  
Italy

Office:  
Fax:  
Email:



Alternate Contact:



United States

Office:  
Fax:  
Email:



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

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.

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

## **8.0                    Statistical Methods and Determination of Sample Size**

### **8.1                    Statistical and Analytical Plans**

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission

will be conducted. 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 Week 12 database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

### **8.1.1                   Analysis Populations**

#### **8.1.1.1               Full Analysis Set (FAS)**

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

#### **8.1.1.2               Per Protocol Analysis Set**

The Per-Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not meet any major protocol violations during the study. Definitions of major protocol violations will be detailed in the SAP. Additional analysis may be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol violations.

#### **8.1.1.3               Safety Analysis Set**

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

### **8.1.2                   Subject Accountability, Disposition and Study Drug Exposure**

#### **8.1.2.1               Subject Accountability**

The following will be summarized by site and by treatment group as well as overall separately for Period 1 and Period 2: number of subjects randomized, the number of

subjects who received at least one dose of study drug, the number of subjects who completed the study, and the number of subjects who prematurely discontinued.

#### **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, and completed the study will be summarized by treatment group and overall. Reasons for premature discontinuation of study drug will be summarized 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 Period 1 alone as well as for Period 1 and Period 2 combined. The exposure to study drug (days) will be summarized with the mean, standard deviation, median, and range for each treatment group. The exposure to study drug is defined as the difference between the dates of the first and last doses of the study drug plus 1 day.

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

#### **8.1.3                Analysis of Demographic and Baseline Characteristics**

Demographic and baseline characteristics will be summarized by treatment group and overall for the FAS. For the purpose of this analysis, baseline data for each subject will be the data collected immediately prior to the first dose of study drug in Period 1.

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

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

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

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

### **8.1.4 Efficacy Analysis**

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

#### **8.1.4.1 Efficacy Analysis for Period 1**

For all efficacy analysis in Period 1, the three placebo groups (Groups 4, 5 and 6) will be combined and treated as one placebo group for analysis purposes.

##### **8.1.4.1.1 Primary Efficacy Variables**

The primary endpoint in Period 1 (at Week 12) is the proportion of subjects achieving ACR20 response at Week 12. Analysis of the primary endpoint will be conducted on the FAS based on treatment as randomized.

The dose-response relationship among the upadacitinib groups and the combined placebo group will be characterized for ACR20 at Week 12. The dose-response curve will be shown graphically with confidence intervals (CIs) for each dose and a non-flat dose

response relationship will be demonstrated using Cochran-Armitage test. The statistical test will be at two-sided significance level of 0.05.

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

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

#### **8.1.4.1.2 Key Secondary Efficacy Variables**

Key secondary endpoints (at Week 12) are listed in Section [5.3.3.1.2](#):

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

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons for each of the upadacitinib treatment groups and the combined placebo group will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates.

See Section [8.1.4.1.5](#) for imputation methods.

#### **8.1.4.1.3 Other Efficacy Variables**

Additional secondary efficacy variables are listed in Section [5.3.3.1.3](#) and will be summarized for all visits. For binary endpoints, frequencies and percentages will be

reported for each treatment group. For continuous endpoints, the change from baseline mean, standard deviation, median, and range will be reported for each treatment group.

#### **8.1.4.1.4      Multiplicity Control for the Primary and Key Secondary Endpoints**

Multiplicity on the primary endpoint is controlled via using the Cochran-Armitage test across the multiple doses. Nominal pairwise comparison of each upadacitinib dose to placebo is also performed as supportive information.

#### **8.1.4.1.5      Imputation Methods**

The following methods will be used for missing data imputation:

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

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

**Non-Responder Imputation (NRI):** NRI applies to binary endpoints only. In NRI analysis, subjects who prematurely discontinue the 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 analysis 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 [5.3.3.1.3](#) and will be summarized for all visits.

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

### **8.1.5            Safety Analyses**

#### **8.1.5.1            General Considerations**

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

Missing safety data will not be imputed.

#### **8.1.5.2            Analysis of Adverse Events**

Unless otherwise specified, the following conventions apply for both the Period 1 safety analysis and the combined safety analysis of Period 1 and Period 2.

### **8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)**

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

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

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

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

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

TEAEs will be summarized and presented by system organ classes (SOCs) and preferred terms (PTs) using MedDRA. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

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

The AEs of special interest (including but not limited to serious infection, opportunistic infection, malignancy, non-melanoma skin cancer (NMSC), malignancy other than NMSC, lymphoma, hepatic disorder, gastrointestinal perforation, anemia, neutropenia, lymphopenia, herpes zoster, increased CPK, renal dysfunction, tuberculosis, adjudicated cardiovascular events and embolic and thrombotic events (non-cardiac, non-CNS) will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the combined safety analysis of Period 1 and Period 2.

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

#### **8.1.5.2.2      Serious Adverse Events and Death**

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

#### **8.1.5.3      Analysis of Laboratory, Vital Sign, and ECG Data**

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

Baseline values are defined as the last non-missing measurements recorded on or before the date of the first dose of study drug in Period 1.

The laboratory data will be categorized as Grade 1, Grade 2, Grade 3 and Grade 4 according to OMERACT criteria (Rheumatology Common Toxicity Criteria V.2.0). For creatine phosphokinase and serum creatinine, NCI CTC criteria will be used. The shift tables will tabulate the number and percentage of subjects with baseline and post-baseline values by grade level.

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

**8.1.6****Pharmacokinetic and Exposure-Response Analyses**

Individual upadacitinib plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods. For subjects enrolled in the intensive pharmacokinetic assessment, pharmacokinetic parameter values of upadacitinib will be tabulated for each subject and each regimen, and summary statistics will be computed for each sampling time and each parameter by regimen.

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.

**8.1.7****Statistical Analysis of Biomarker Data**

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

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

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## 8.2 Determination of Sample Size

Sample size was estimated based on the previous global Phase 2 trial (Study M13-537). Assuming an ACR20 response rate of 46% for placebo group, 62% for low dose group (7.5 mg QD), 68% for middle dose group (15 mg QD) and 80% for high dose group (30 mg QD) of upadacitinib, the sample size to have 90% power and two-sided alpha of 5% to detect a statistically significant dose-response using Cochran-Armitage test will be 42 subjects per group. And the sample size to demonstrate the superiority of upadacitinib compared to placebo will be 46 subjects to provide the 90% power and 5% of two-sided alpha. Taking 5% of drop-out rate into consideration, sample size will be 48 per group (total sample size: 192 subjects).

## 8.3 Randomization Methods

Subjects will be randomly assigned in a 3:3:3:1:1:1 ratio to one of the six treatment groups:

- Group 1: upadacitinib 7.5 mg QD (N = 48) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 2: upadacitinib 15 mg QD (N = 48) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 3: upadacitinib 30 mg QD (N = 48) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → upadacitinib 30 mg QD (Period 2)

Randomization will be stratified by prior exposure to bDMARD (yes/no).

See Section [5.5.3](#) for details.

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

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

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

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

**9.2            Ethical Conduct of the Study**

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

**9.3****Subject Information and Consent**

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. In Japan, if a subject is below 20 years old, the subject's or legal guardian must be explained and willing to give written informed consent. A copy of the informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

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

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker

samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

### **9.3.1                    Informed Consent Form and Explanatory Material**

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

### **9.3.2                    Revision of the Consent Form and Explanatory Material**

In Japan, when important new information related to the subject's consent becomes available, the Principal Investigator will revise the informed consent and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The Investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

## **10.0                    Source Documents and Case Report Form Completion**

### **10.1                    Source Documents**

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

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

## **10.2 Case Report Forms**

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from

investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

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

- The following data are being collected with an Electronic Patient-Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA:
  - Completed by Patient:
    - Patient's Global Assessment of Disease Activity VAS
    - Patient's Assessment of Pain VAS
    - HAQ-DI
    - EQ-5D-5L
    - SF-36
    - FACIT-F
    - RA-WIS
  - Completed by Site:
    - Physician's 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.

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

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

The ePRO data will be collected by the following method:

*Tablet based*

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

## **11.0 Data Quality Assurance**

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

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

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

Routine hematology, serum chemistry and serology, and urinalysis, and other tests such as rheumatoid factor, anti-CCP, and HBV/HCV testing, will be conducted using a central laboratory (refer to [Table 2](#) and [Table 4](#)). The data from these analyses will be electronically transferred from the central laboratory to the study database.

Laboratory tests including, but not limited to, urine pregnancy testing and ESR, will be conducted locally by each study site (refer to [Table 2](#) and [Table 4](#)). Sites will provide AbbVie with laboratory certifications and normal ranges for each local laboratory used.

The full name, address, phone number and fax number for each local laboratory will also be included.

## **12.0      Use of Information**

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

research/validation information data will be published or presented only in a way that does not identify any individual subject.

## **13.0                   Completion of the Study**

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (Director of the Site in Japan) and AbbVie. The investigator will provide a final report to the Director of the Site following conclusion of the study. Upon provided the report, the Director of the Site will notify AbbVie or their representative and IEC/IRB of the conclusion of the study in Japan.

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

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

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

## **14.0                   Investigator's Agreement**

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

Protocol Title: A Phase 2b/3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs

Protocol Date: 23 February 2018

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Signature of Principal Investigator

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Date

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Name of Principal Investigator (printed or typed)

## 15.0 Reference List

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## **Appendix A. Responsibilities of the Clinical Investigator**

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section **14.0** of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

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**Appendix B. List of Protocol Signatories**

Name	Title	Functional Area
		Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacokinetics and Pharmacodynamics
		Bioanalysis
		Clinical Program Development
		Japan Development
		Japan Development

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## Appendix C. Physician's Global Assessment of Disease Activity Example

### Visual Analog Scale (VAS)

VAS will be used to assess the physician's global assessment of disease activity. 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).



**Appendix D. 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	
1. Temporomandibular	0	1	0	1	9	NA	0	1	0	1	9	NA
2. Sternoclavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
3. Acromio-clavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
4. Shoulder	0	1	0	1	9	NA	0	1	0	1	9	NA
5. Elbow	0	1	0	1	9	NA	0	1	0	1	9	NA
6. Wrist	0	1	0	1	9	NA	0	1	0	1	9	NA
7. Metacarpophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
8. Metacarpophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
9. Metacarpophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
10. Metacarpophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
11. Metacarpophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
12. Thumb Interphalangeal	0	1	0	1	9	NA	0	1	0	1	9	NA
13. Prox. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
14. Prox. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
15. Prox. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
16. Prox. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
17. Distal Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
18. Distal Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
19. Distal Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
20. Distal Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
21. Hip	0	1	--	--	9	NA	0	1	--	--	9	NA
22. Knee	0	1	0	1	9	NA	0	1	0	1	9	NA
23. Ankle	0	1	0	1	9	NA	0	1	0	1	9	NA
24. Tarsus	0	1	0	1	9	NA	0	1	0	1	9	NA
25. Metatarsophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
26. Metatarsophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
27. Metatarsophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA

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	
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 E. Latent TB Risk Assessment Form Example**

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
  - Sub-Saharan Africa
  - India
  - China
  - Mexico
  - Southeast Asia or Micronesia
  - The former Soviet Union
3. Have you lived or worked in a prison, homeless shelter, immigration center, or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
  - Chronic Cough
  - Production of Sputum
  - Blood-Streaked Sputum
  - Unexplained Weight Loss
  - Fever
  - Fatigue/Tiredness
  - Night Sweats
  - Shortness of Breath

From: <http://www.mayoclinic.com/health/tuberculosis/DS00372/DSECTION=risk-factors>  
[http://www.in.gov/fssa/files/Tuberculosis\\_Questionnaire.pdf](http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf)

## Appendix F. Patient's Global Assessment of Disease Activity Example

## **Visual Analog Scale (VAS)**

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

- *Subject's global assessment of disease activity (within last 24 hours)*

The subject will rate the severity of the RA symptoms and how he/she is doing from 0 to 100. This assessment will be used for the DAS28 (CRP) calculation in this study (see example below):

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



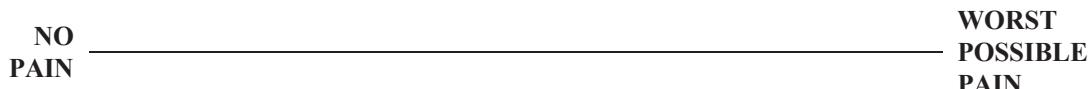
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**Appendix G. Patient's Assessment of Pain Example****Visual Analog Scale (VAS)**

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

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

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



---

**Appendix H. Health Assessment Questionnaire (HAQ-DI) Example****HEALTH ASSESSMENT QUESTIONNAIRE**

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

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

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

**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:**

<input type="checkbox"/> Dressing and Grooming	<input type="checkbox"/> Eating
<input type="checkbox"/> Arising	<input type="checkbox"/> Walking

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

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

**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:**

<input type="checkbox"/> Hygiene	<input type="checkbox"/> Gripping and opening things
<input type="checkbox"/> Reach	<input type="checkbox"/> Errands and chores

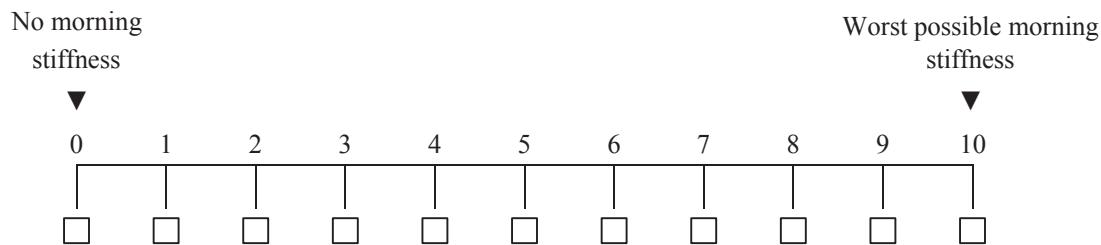
HAQ – United States/English

HAQ-DI\_AU1.0-eng-USori.doc © Stanford University

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**Appendix I. Patient's Assessment of Severity and Duration of Morning Stiffness Example****Instructions:**

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



When you experience morning stiffness, how long does it take to get as limber as possible: \_\_\_\_ hours \_\_\_\_ minutes

---

**Appendix J. EuroQoL-5D Example**

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

**Mobility**

I have no problems walking	<input type="checkbox"/>
I have slight problems walking	<input type="checkbox"/>
I have moderate problems walking	<input type="checkbox"/>
I have severe problems walking	<input type="checkbox"/>
I am unable to walk	<input type="checkbox"/>

**Self-Care**

I have no problems washing or dressing myself	<input type="checkbox"/>
I have slight problems washing or dressing myself	<input type="checkbox"/>
I have moderate problems washing or dressing myself	<input type="checkbox"/>
I have severe problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>

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

I have no problems with doing my usual activities	<input type="checkbox"/>
I have slight problems with doing my usual activities	<input type="checkbox"/>
I have moderate problems with doing my usual activities	<input type="checkbox"/>
I have severe problems with doing my usual activities	<input type="checkbox"/>
I am unable to do my usual activities	<input type="checkbox"/>

---

**Pain/Discomfort**

I have no pain or discomfort	<input type="checkbox"/>
I have slight pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have severe pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>

**Anxiety/Depression**

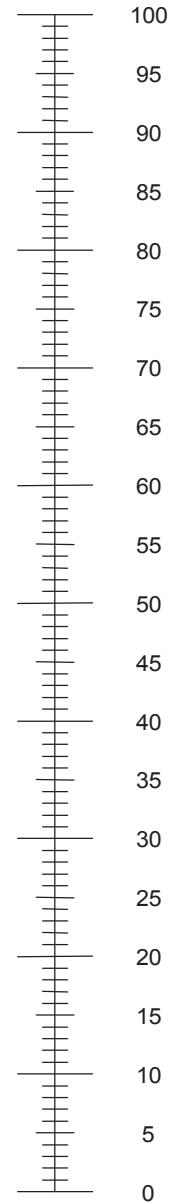
I am not anxious or depressed	<input type="checkbox"/>
I am slightly anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am severely anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

---

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

YOUR HEALTH TODAY =

The best health  
you can imagine



The worst health  
you can imagine

---

**Appendix K. Short Form-36 (SF-36™) Health Status Survey Questionnaire Example****Your Health and Well-Being**

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

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

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

Excellent	Very good	Good	Fair	Poor
<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 Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3

b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3

c Lifting or carrying groceries 1 2 3

d Climbing several flights of stairs 1 2 3

e Climbing one flight of stairs 1 2 3

f Bending, kneeling, or stooping 1 2 3

g Walking more than a mile 1 2 3

h Walking several hundred yards 1 2 3

i Walking one hundred yards 1 2 3

j Bathing or dressing yourself 1 2 3

---

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time

<sup>a</sup> Cut down on the amount of time you spent on work or other activities  1  2  3  4  5

<sup>b</sup> Accomplished less than you would like  1  2  3  4  5

<sup>c</sup> Were limited in the kind of work or other activities  1  2  3  4  5

<sup>d</sup> Had difficulty performing the work or other activities (for example, it took extra effort)  1  2  3  4  5

---

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼

<sup>a</sup> Cut down on the amount of time you spent on work or other activities 1 2 3 4 5

<sup>b</sup> Accomplished less than you would like 1 2 3 4 5

<sup>c</sup> Did work or other activities less carefully than usual 1 2 3 4 5

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

	Not at all	Slightly	Moderately	Quite a bit	Extremely
	▼	▼	▼	▼	▼
	<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 
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

<sup>a</sup> Did you feel full of life?

<sup>b</sup> Have you been very nervous?

<sup>c</sup> Have you felt so down in the dumps that nothing could cheer you up?

<sup>d</sup> Have you felt calm and peaceful?

<sup>e</sup> Did you have a lot of energy?

<sup>f</sup> Have you felt downhearted and depressed?

<sup>g</sup> Did you feel worn out?

<sup>h</sup> Have you been happy?

<sup>i</sup> Did you feel tired?

---

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 
<sup>a</sup> 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
<sup>b</sup> 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
<sup>c</sup> 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
<sup>d</sup> 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 L. Functional Assessment of Chronic Illness Therapy – Fatigue  
(FACIT-F) Scale Example**

Below is a list of statements that other people with your illness have said are important.

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		A				
		Not at all	little bit	Some- what	Quite a bit	Very much
HI7	I feel fatigued .....	0	1	2	3	4
HI12	I feel weak all over .....	0	1	2	3	4
An1	I feel listless ("washed out") .....	0	1	2	3	4
An2	I feel tired .....	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy .....	0	1	2	3	4
An7	I am able to do my usual activities .....	0	1	2	3	4
An8	I need to sleep during the day .....	0	1	2	3	4
An12	I am too tired to eat .....	0	1	2	3	4
An14	I need help doing my usual activities .....	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to .....	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4
.....						

**Appendix M. Work Instability Scale for RA (RA-WIS) Example**

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

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**Appendix N.     Rheumatology Common Toxicity Criteria v.2.0 Example**

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

**Rheumatology Common Toxicity Criteria v2.0**

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

<b>1 – Mild</b>				<b>2 – Moderate</b>				<b>3 – Severe</b>				<b>4 – Includes Life Threatening</b>				
Asymptomatic, or transient	Symptomatic	Prolonged symptoms, reversible, major functional impairment	At risk of death	Short duration (< 1 week)	Duration (1 – 2 weeks)	Prescription meds/partial relief	Substantial disability, especially if permanent.	Alter lifestyle occasionally	May be hospitalized < 24 hr	Multiple meds	Hospitalised > 24 hr	Temporary study drug discontinuation, or/and dose reduced	Study drug discontinued			
<b>A. Allergic/Immunologic</b>																
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													
A2. Autoimmune reaction	Serologic 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)													
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med. Required, slow	Corticosteroids or other prescription med with persistent disabling symptoms such as impaired exercise tolerance													
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													

<b>A. Allergic/Immunologic (continued)</b>				
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>B. Cardiac</b>				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalisation required, parenteral meds
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g., 1 + feet/calves), self-limited, no therapy required	Symptomatic (e.g., 2 + feet/calves), requires therapy	Symptoms limiting function (e.g., 3 + feet/calves, 2 + thighs), partial relief with treatment prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, transient increase by > 20 mmHg (diastolic) or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100 or by > 10 mmHg (diastolic), requiring and responding readily to treatment	Symptomatic increase > 150/100, > 20 mmHg, persistent, requiring multi agency therapy, difficult to control	Hypertensive crisis
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure > 20 mmHg	Symptomatic, without interference with function, recurrent or persistent > 20 mmHg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischaemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain; transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrhythmia or/and CHF

<b>B. Cardiac (continued)</b>			
B7. Pericarditis/ pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic NSAID required	Detectable on chest x-ray, dyspnoea; or pericardioscopy; requires corticosteroids
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
<b>C. General (Constitutional)</b>			
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
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
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
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling
C7. Weight gain	5% – 9.9%	10% – 19.9%	20% – 30%
C8. Weight loss	5% – 9.9%	10% – 19.9%	20% – 30%
Pulsus alternates with low cardiac output; requires surgery			
Pulmonary embolism			
Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation			
Intractable, debilitating, requires parenteral meds.			
Debilitating, hospitalisation; no relief with meds			
Debilitating, hospitalisation; no relief with meds			
Dehydration, requiring IV fluids/hospitalization > 24 hrs			
NA			
NA			

<b>D. Dermatologic</b>					
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 systemic 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	
<b>E. Ear/Nose/Throat</b>					
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	

<b>E. Ear/Nose/Throat (continued)</b>					
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 duration	
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition	
<b>F. Eye/Ophthalmologic</b>					
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	

<b>F. Eye/Ophthalmologic (continued)</b>			
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
F6. Xerophthalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration
<b>G. Gastrointestinal</b>			
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention
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.
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
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion $\leq 2$ units needed; responds to treatment	Haematemesis, transfusion 3 – 4 units, prolonged interference with function
G6. Haematochezia (rectal bleeding)	Haemorrhoidal, asymptomatic, no transfusion	Symptomatic, transfusion $\leq 2$ units, reversible	Recurrent, transfusion $> 3 – 4$ units
			$> 4$ units, hypotension, requiring hospitalization

<b>G. Gastrointestinal (continued)</b>				
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	Amylase 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.
<b>H. Musculoskeletal</b>				
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

<b>I. Neuropsychiatric</b>			
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
12. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events
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
14. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor
15. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause
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
17. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship
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
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 paraesthesia interfering with function
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

<b>I. Neuropsychiatric (continued)</b>				
111. 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
<b>J. Pulmonary</b>				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O <sub>2</sub>	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 <sub>2</sub> relieves	Symptomatic at rest, debilitating, requires constant nasal O <sub>2</sub>
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 <sub>2</sub>	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

<b>Laboratory Data</b>				
<b>K. Haematology</b>				
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
<b>L. Chemistry</b>				
L1. Hypocalcaemia (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; Grade4: > 6.0 × ULN

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## Appendix O. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

### Global Protocol Changes

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

### Specific Protocol Changes

#### **Section 1.0 Title Page**

"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency  
Contact:

[REDACTED]

Office:  
Mobile:  
Email:

AbbVie Inc.

[REDACTED]  
Redwood City, CA 94063

Has been changed to read:

Sponsor/Emergency  
Contact:

[REDACTED]

Office:  
Mobile:  
Email:  
Emergency 24-hour Number:

AbbVie Deutschland GmbH &  
Co. KG  
Knollstrasse – [REDACTED]  
67061 Ludwigshafen  
Germany

#### **Section 1.2 Synopsis**

Previously read:

<b>AbbVie GK.</b>	<b>Protocol Number:</b> M14-663
<b>Name of Study Drug:</b> ABT-494	<b>Phase of Development:</b> 2b/3
<b>Name of Active Ingredient:</b> ABT-494	<b>Date of Protocol Synopsis:</b> 21 November 2016
<b>Protocol Title:</b> A Phase 2b/3, Randomized, Double-Blind Study Comparing ABT-494 to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs	

**Objectives:****Period 1**

1. To confirm dose response in the efficacy of ABT-494 7.5 mg QD, 15 mg QD and 30 mg QD, and to compare the efficacy of ABT-494 versus placebo for the treatment of signs and symptoms of Japanese subjects with moderately to severely active rheumatoid arthritis (RA) who are on a stable dose of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and have an inadequate response to csDMARDs.
2. To compare the safety and tolerability of ABT-494 7.5 mg QD, 15 mg QD and 30mg QD versus placebo in Japanese subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.

**Period 2**

To evaluate the long-term safety, tolerability, and efficacy of ABT-494 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.

**Investigators:** Multicenter**Study Sites:** Approximately 52

**Study Population:** Adult female and male subjects who are at least 18 years of age with a diagnosis of RA for  $\geq$  3 months who also fulfill the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have  $\geq$  6 swollen joints (based on 66 joint counts) and  $\geq$  6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP)  $\geq$  3 mg/L (central lab) at Screening. Subjects must have been on a stable dose of csDMARD therapy (methotrexate [MTX], sulfasalazine, leflunomide, bucillamine or ildaritimod) for  $\geq$  4 weeks prior to the first dose of study drug.

**Number of Subjects to be Enrolled:** Approximately 192**Methodology:**

This is a Phase 2b/3 multicenter study that includes two periods. Period 1 is a 12-week randomized, double-blind, parallel-group, placebo-controlled period designed to confirm dose response in the efficacy of ABT-494 7.5 mg QD, 15 mg QD and 30 mg QD and to compare the safety and efficacy of ABT-494 versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of ABT-494 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.

**Methodology (Continued):**

The study duration will include a 35-day screening period; a 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a blinded long-term extension period (until regulatory approval of RA indication in Japan) (Period 2); and a 30-day follow-up period. Subjects who meet eligibility criteria will be randomized in a 3:3:3:1:1:1 ratio to one of six treatment groups:

- Group 1: ABT-494 7.5 mg QD (N = 48) (Period 1) → ABT-494 7.5 mg QD (Period 2)
- Group 2: ABT-494 15 mg QD (N = 48) (Period 1) → ABT-494 15 mg QD (Period 2)
- Group 3: ABT-494 30 mg QD (N = 48) (Period 1) → ABT-494 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → ABT-494 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → ABT-494 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → ABT-494 30 mg QD (Period 2)

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

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

Starting at Week 24 (after Week 24 assessments have been performed), initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or adding or increasing doses of csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label. Starting at Week 24 and thereafter, subjects who fail to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits (see Section 5.2.3.1) will be discontinued from the study. For RA flare treatment, no more than 3 consecutive days of systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Subjects taking MTX should take oral folic acid throughout study participation. Folic acid dosing and timing of regimen will be based on the Investigator's discretion.

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

Subjects who complete the Week 12 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2, until the regulatory approval of the RA indication in Japan. Subjects who are assigned to ABT-494 treatment groups in Period 1 will continue to receive ABT-494 7.5 mg QD, 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner. Subjects who are assigned to placebo in Period 1 will be switched to receive ABT-494 7.5 mg QD, 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments.

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

**Diagnosis and Main Criteria for Inclusion/Exclusion:****Main Inclusion:**

1. Adult male or female, at least 18 years old.
2. Diagnosis of RA for  $\geq$  3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects have been receiving csDMARD therapy  $\geq$  3 months and on a stable dose for  $\geq$  4 weeks prior to the first dose of study drug.
  - Subjects must have failed (lack of efficacy) at least one of the following: MTX, sulfasalazine, leflunomide, bucillamine or iguratimod.
  - The following csDMARDs are allowed (stable dose for  $\geq$  4 weeks prior to the first dose of study drug): oral or parenteral MTX (7.5 mg – 25 mg/week. 7.5 mg minimum applies only if MTX is taken alone without other csDMARDs; no minimum MTX dose is required if MTX is combined with another csDMARD), sulfasalazine ( $\leq$  3000 mg/day), leflunomide ( $\leq$  20 mg/day), bucillamine ( $\leq$  300 mg/day) and iguratimod ( $\leq$  50 mg/day).
  - A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
4. Subject meets both of the following disease activity criteria:
  - a.  $\geq$  6 swollen joints (based on 66 joint counts) and  $\geq$  6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
  - b. High-sensitivity C-reactive protein (hsCRP)  $\geq$  3 mg/L (central lab) at the Screening Visit.
5. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of total number of subjects) after the required washout period. Specifically, prior to enrollment:
  - a. Subjects with limited exposure to bDMARD ( $<$  3 months) OR
  - b. Subjects who are responding to bDMARD therapy but had to discontinue due to intolerance (regardless of treatment duration).

**Main Exclusion:**

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Subjects who are considered inadequate responders (lack of efficacy) to bDMARD therapy, after minimum 3 months treatment, as determined by the Investigator.
3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis [SpA] 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.
4. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase  $>$  2  $\times$  upper limit of normal (ULN); serum alanine transaminase  $>$  2  $\times$  ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula  $<$  40 mL/min/1.73 m<sup>2</sup>; total white blood cell count  $<$  2,500/ $\mu$ L; absolute neutrophil count  $<$  1,500/ $\mu$ L; platelet count  $<$  100,000/ $\mu$ L; absolute lymphocyte count  $<$  800/ $\mu$ L; and hemoglobin  $<$  10 g/dL.

<b>Investigational Product:</b>	ABT-494
<b>Doses:</b>	7.5 mg QD 15 mg QD 30 mg QD
<b>Mode of Administration:</b>	Oral
<b>Reference Therapy:</b>	Matching placebo for ABT-494 QD
<b>Dose:</b>	N/A
<b>Mode of Administration:</b>	Oral
<b>Duration of Treatment:</b>	Period 1: 12 weeks; Period 2: up to the regulatory approval of RA indication in Japan
<b>Criteria for Evaluation:</b>	
<b>Efficacy:</b>	
<b>Period 1</b>	
	The primary endpoint is the proportion of subjects achieving ACR20 response at Week 12. ACR20 response rate will be determined based on 20% or greater improvement in Tender Joint Count (TJC) and Swollen Joint Count (SJC) and $\geq 3$ 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.
	Key Secondary endpoints (at Week 12) are:
	1. Change from baseline in DAS28 (CRP); 2. Change from baseline in HAQ-DI; 3. ACR50 response rate; 4. ACR70 response rate; 5. Change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS); 6. Proportion of subjects achieving Proportion of subjects achieving Low Disease Activity (LDA) defined as Disease Activity Score (DAS) 28 (C-reactive protein [CRP]) $\leq 3.2$ ; 7. Proportion of subjects achieving Clinical remission (CR) based on DAS28 (CRP); 8. ACR20 response rate at Week 1; 9. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); 10. Change from baseline in Work Instability Scale for Rheumatoid Arthritis (RA-WIS); 11. Change from baseline in morning stiffness (severity).

**Criteria for Evaluation (Continued):****Efficacy (Continued):**

Additional endpoints at all visits of this study are:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in morning stiffness (severity and duration);
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria (see below);
- Change from baseline in EQ-5D-5L;
- Change from baseline in SF-36.

	<b>DAS28 (CRP) and DAS28 (ESR)</b>	<b>SDAI</b>	<b>CDAI</b>
LDA	$\leq 3.2$	$\leq 11.0$	$\leq 10$
CR	$< 2.6$	$\leq 3.3$	$\leq 2.8$

**Period 2**

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 16, 20, 24, 36, 48, and every 12 weeks thereafter until completion of the study:

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

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

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

**Pharmacokinetic:**

Blood samples for assay of ABT-494 and possibly other concomitant medications in plasma will be collected at Weeks 1, 2, 4, 8 and 12/Premature Discontinuation in Period 1. Additionally, intensive pharmacokinetic assessment will be performed in 32 subjects during one of the study visits, including unscheduled visits occurring after Week 1, in either Periods 1 or 2 excluding Baseline and Premature Discontinuation visit. For Subjects in the intensive pharmacokinetic assessment, blood samples will be collected during the study visit chosen for intensive pharmacokinetic (PK) assessment prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose.

**Criteria for Evaluation (Continued):****In Vivo Pharmacodynamic Biomarkers (Period 1 and 2)****Period 1**

Change from baseline in lymphocyte subsets (including but not limited to natural killer cells, natural killer T cells, B cells, and T cells) will be evaluated at Baseline, Week 8, Premature Discontinuation visit and 30 days follow-up visit.

**Period 2**

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

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

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

**Safety:**

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

**Statistical Methods:****Efficacy:**

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, and efficacy analyses are based on the treatment to which subjects are randomized.

**Period 1 Efficacy****Analysis of the Primary and Key Secondary Endpoints:****Primary Efficacy Analysis:**

The dose-response relationship among the ABT-494 groups and the combined placebo group will be characterized for the ACR20 response rate at Week 12. The dose-response curve will be shown graphically with confidence intervals for each dose and a non-flat dose response relationship will be demonstrated using Cochran-Armitage test. The response rates of ACR20 of each ABT-494 group will be compared with the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for main stratification factors.

**Key Secondary Efficacy Analysis:**

The key secondary efficacy endpoints (at Week 12) will be evaluated. For a list of the key secondary endpoints, see "Efficacy" part in "Criteria for Evaluation."

All nominal statistical comparisons of ABT-494 versus placebo for the primary and key secondary endpoints and for the three doses will be conducted using a two-sided significance level of 0.05.

For the analysis of binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparisons between each ABT-494 group and the combined placebo groups will be conducted using the Cochran-Mantel-Haenszel test adjusting for main stratification factors.

**Statistical Methods (Continued):****Efficacy (Continued)****Period 1 Efficacy (Continued)****Key Secondary Efficacy Analysis (Continued):**

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between each of the ABT-494 treatment groups and the combined placebo groups will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates.

Non-responder imputation approach will serve as the primary analysis approach for key binary endpoints, and multiple imputation will serve as the primary analysis approach for key continuous endpoints. Sensitivity analyses based on observed cases will also be conducted for key endpoints.

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

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

**Pharmacokinetic:**

A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of ABT-494 oral clearance (CL/F) and volume of distribution (V/F).

For the subjects participating in the intensive pharmacokinetic assessment, the following ABT-494 parameters will be estimated using noncompartmental methods:

- The maximum observed concentration ( $C_{\max}$ ),
- The time to  $C_{\max}$  (peak time,  $T_{\max}$ ),
- The area under the plasma concentration-time curve (AUC),
- The apparent oral clearance (CL/F),
- Plasma concentration at the end of dosing interval ( $C_{\text{trough}}$ )
- The minimum plasma concentration over a 24-hour period at steady state ( $C_{\min}$ )

Additional parameters may be estimated if useful in the interpretation of the data.

**Safety:**

Safety analyses will be carried out using the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug. Analyses will be conducted for Period 1 alone, as well as for Period 1 and Period 2 combined.

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

**Has been changed to read:**

<b>AbbVie GK.</b>	<b>Protocol Number:</b> M14-663
<b>Name of Study Drug:</b> Upadacitinib	<b>Phase of Development:</b> 2b/3
<b>Name of Active Ingredient:</b> Upadacitinib	<b>Date of Protocol Synopsis:</b> 23 February 2018
<b>Protocol Title:</b> A Phase 2b/3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs	
<b>Objectives:</b>	
<b>Period 1</b>	
1. To confirm dose response in the efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD, and to compare the efficacy of upadacitinib versus placebo for the treatment of signs and symptoms of Japanese subjects with moderately to severely active rheumatoid arthritis (RA) who are on a stable dose of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and have an inadequate response to csDMARDs.	
2. To compare the safety and tolerability of upadacitinib 7.5 mg QD, 15 mg QD and 30mg QD versus placebo in Japanese subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs.	
<b>Period 2</b>	
To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.	
<b>Investigators:</b> Multicenter	
<b>Study Sites:</b> Approximately 52	
<b>Study Population:</b> Adult female and male subjects who are at least 18 years of age with a diagnosis of RA for $\geq$ 3 months who also fulfill the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. Eligible study subjects must have $\geq$ 6 swollen joints (based on 66 joint counts) and $\geq$ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits, and high-sensitivity C-reactive protein (hsCRP) $\geq$ 3 mg/L (central lab) at Screening. Subjects must have been on a stable dose of csDMARD therapy (methotrexate [MTX], sulfasalazine, leflunomide, bucillamine or iguratimod) for $\geq$ 4 weeks prior to the first dose of study drug.	
<b>Number of Subjects to be Enrolled:</b> Approximately 192	
<b>Methodology:</b>	
This is a Phase 2b/3 multicenter study that includes two periods. Period 1 is a 12-week randomized, double-blind, parallel-group, placebo-controlled period designed to confirm dose response in the efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD and to compare the safety and efficacy of upadacitinib versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of csDMARDs and have an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD, 15 mg QD and 30 mg QD in subjects with RA who have completed Period 1.	

**Methodology (Continued):**

The study duration will include a 35-day screening period; a 12-week randomized, double-blind, parallel-group, placebo controlled treatment period (Period 1); a blinded long-term extension period (until regulatory approval of RA indication in Japan) (Period 2); and a 30-day follow-up period. Subjects who meet eligibility criteria will be randomized in a 3:3:3:1:1:1 ratio to one of six treatment groups:

- Group 1: upadacitinib 7.5 mg QD (N = 48) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 2: upadacitinib 15 mg QD (N = 48) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 3: upadacitinib 30 mg QD (N = 48) (Period 1) → upadacitinib 30 mg QD (Period 2)
- Group 4: Placebo (N = 16) (Period 1) → upadacitinib 7.5 mg QD (Period 2)
- Group 5: Placebo (N = 16) (Period 1) → upadacitinib 15 mg QD (Period 2)
- Group 6: Placebo (N = 16) (Period 1) → upadacitinib 30 mg QD (Period 2)

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

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

Starting at Week 24 (after Week 24 assessments have been performed), initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, low potency analgesics or csDMARDs (restricted to oral or parenteral MTX, sulfasalazine, leflunomide, bucillamine or iguratimod and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label. Starting at Week 24, at least 20% improvement in BOTH SJC AND TJC compared to baseline is required to remain in the study. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) (see Section 5.2.3.2 for permitted concomitant therapy), must be discontinued from the study. For RA flare treatment, no more than 3 consecutive days of systemic corticosteroids (maximum dose of 0.5 mg/kg/day of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Subjects taking MTX should take oral folic acid throughout study participation. Folic acid dosing and timing of regimen will be based on the Investigator's discretion.

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

Subjects who complete the Week 12 visit (end of Period 1) will enter the blinded long-term extension portion of the study, Period 2, until the regulatory approval of the RA indication in Japan. Subjects who are assigned to upadacitinib treatment groups in Period 1 will continue to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD per original randomization assignment in a blinded manner.

**Methodology (Continued):**

Subjects who are assigned to placebo in Period 1 will be switched to receive upadacitinib 7.5 mg QD, 15 mg QD or 30 mg QD in a blinded fashion per pre-specified randomization assignments.

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission will be conducted. Study sites and subjects will remain blinded for the duration 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  $\geq$  3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA.
3. Subjects have been receiving csDMARD therapy  $\geq$  3 months and on a stable dose for  $\geq$  4 weeks prior to the first dose of study drug.
  - Subjects must have failed (lack of efficacy) at least one of the following: MTX, sulfasalazine, leflunomide, bucillamine or iguratimod.
  - The following csDMARDs are allowed (stable dose for  $\geq$  4 weeks prior to the first dose of study drug): oral or parenteral MTX (7.5 mg – 25 mg/week. 7.5 mg minimum applies only if MTX is taken alone without other csDMARDs; no minimum MTX dose is required if MTX is combined with another csDMARD), sulfasalazine ( $\leq$  3000 mg/day), leflunomide ( $\leq$  20 mg/day), bucillamine ( $\leq$  300 mg/day) and iguratimod ( $\leq$  50 mg/day).
  - A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
4. Subject meets both of the following disease activity criteria:
  - a.  $\geq$  6 swollen joints (based on 66 joint counts) and  $\geq$  6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
  - b. High-sensitivity C-reactive protein (hsCRP)  $\geq$  3 mg/L (central lab) at the Screening Visit.
5. Subjects with prior exposure to at most one bDMARD may be enrolled (up to 20% of total number of subjects) after the required washout period. Specifically, prior to enrollment:
  - a. Subjects with limited exposure to bDMARD ( $<$  3 months) OR
  - b. Subjects who are responding to bDMARD therapy but had to discontinue due to intolerance (regardless of treatment duration).

**Main Exclusion:**

1. Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).
2. Subjects who are considered inadequate responders (lack of efficacy) to bDMARD therapy, after minimum 3 months treatment, as determined by the Investigator.
3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis [SpA] 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.

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

4. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug: serum aspartate transaminase  $> 2 \times$  upper limit of normal (ULN); serum alanine transaminase  $> 2 \times$  ULN; estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula  $< 40 \text{ mL/min}/1.73 \text{ m}^2$ ; total white blood cell count  $< 2,500/\mu\text{L}$ ; absolute neutrophil count  $< 1,500/\mu\text{L}$ ; platelet count  $< 100,000/\mu\text{L}$ ; absolute lymphocyte count  $< 800/\mu\text{L}$ ; and hemoglobin  $< 10 \text{ g/dL}$ .

**Investigational Product:** Upadacitinib**Doses:**  
7.5 mg QD  
15 mg QD  
30 mg QD**Mode of Administration:** Oral**Reference Therapy:** Matching placebo for upadacitinib QD**Dose:** N/A**Mode of Administration:** Oral**Duration of Treatment:** Period 1: 12 weeks; Period 2: up to the regulatory approval of RA indication in Japan**Criteria for Evaluation:****Efficacy:****Period 1**

The primary endpoint is the proportion of subjects achieving ACR20 response at Week 12.

ACR20 response rate will be determined based on 20% or greater improvement in Tender Joint Count (TJC) and Swollen Joint Count (SJC) and  $\geq 3$  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.

Key Secondary endpoints (at Week 12) are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. ACR50 response rate;
4. ACR70 response rate;
5. Change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS);
6. Proportion of subjects achieving Low Disease Activity (LDA) defined as Disease Activity Score (DAS) 28 (C-reactive protein [CRP])  $\leq 3.2$ ;
7. Proportion of subjects achieving Clinical remission (CR) based on DAS28 (CRP);
8. ACR20 response rate at Week 1;
9. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F);
10. Change from baseline in Work Instability Scale for Rheumatoid Arthritis (RA-WIS);
11. Change from baseline in morning stiffness (severity).

**Criteria for Evaluation (Continued):****Efficacy (Continued):**

Additional endpoints at all visits of this study are:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in DAS28 (CRP) and DAS28 (erythrocyte sedimentation rate [ESR]);
- Change from baseline in morning stiffness (severity and duration);
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) criteria (see below);
- Change from baseline in EQ-5D-5L;
- Change from baseline in SF-36;
- Change from baseline in FACIT-F;
- Change from baseline in RA-WIS.

	<b>DAS28 (CRP) and DAS28 (ESR)</b>	<b>SDAI</b>	<b>CDAI</b>
LDA	$\leq 3.2$	$\leq 11.0$	$\leq 10$
CR	$< 2.6$	$\leq 3.3$	$\leq 2.8$

**Period 2**

Assessments to evaluate efficacy of treatment in Period 2 will be analyzed for the following measures at Weeks 16, 20, 24, 36, 48, and every 12 weeks thereafter until completion of the study:

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

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

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

**Criteria for Evaluation (Continued):****Pharmacokinetic:**

Blood samples for assay of upadacitinib and possibly other concomitant medications in plasma will be collected at Weeks 1, 2, 4, 8 and 12/Premature Discontinuation in Period 1. Additionally, intensive pharmacokinetic assessment will be performed in approximately 32 subjects during one of the study visits, including unscheduled visits occurring after Week 1, in either Periods 1 or 2 excluding Baseline and Premature Discontinuation visit. For Subjects in the intensive pharmacokinetic assessment, blood samples will be collected during the study visit chosen for intensive pharmacokinetic (PK) assessment prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose.

**In Vivo Pharmacodynamic Biomarkers (Period 1 and 2)****Period 1**

Change from baseline in lymphocyte subsets (including but not limited to natural killer cells, natural killer T cells, B cells, and T cells) will be evaluated at Baseline, Week 8, Premature Discontinuation visit and 30 days follow-up visit.

**Period 2**

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

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

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

**Safety:**

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

**Statistical Methods:****Efficacy:**

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, and efficacy analyses are based on the treatment to which subjects are randomized.

**Period 1 Efficacy****Analysis of the Primary and Key Secondary Endpoints:****Primary Efficacy Analysis:**

The dose-response relationship among the upadacitinib groups and the combined placebo group will be characterized for the ACR20 response rate at Week 12. The dose-response curve will be shown graphically with confidence intervals for each dose and a non-flat dose response relationship will be demonstrated using Cochran-Armitage test. The response rates of ACR20 of each upadacitinib group will be compared with the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for main stratification factors.

**Key Secondary Efficacy Analysis:**

The key secondary efficacy endpoints (at Week 12) will be evaluated. For a list of the key secondary endpoints, see "Efficacy" part in "Criteria for Evaluation."

All nominal statistical comparisons of upadacitinib versus placebo for the primary and key secondary endpoints and for the three doses will be conducted using a two-sided significance level of 0.05.

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

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between each of the upadacitinib treatment groups and the combined placebo groups will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates.

Non-responder imputation approach will serve as the primary analysis approach for key binary endpoints, and multiple imputation will serve as the primary analysis approach for key continuous endpoints.

Sensitivity analyses based on observed cases 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.

**Statistical Methods (Continued):****Pharmacokinetic:**

A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of ABT-494 oral clearance (CL/F) and volume of distribution (V/F).

For the subjects participating in the intensive pharmacokinetic assessment, the following upadacitinib parameters will be estimated using noncompartmental methods:

- The maximum observed concentration ( $C_{\max}$ ),
- The time to  $C_{\max}$  (peak time,  $T_{\max}$ ),
- The area under the plasma concentration-time curve (AUC),
- The apparent oral clearance (CL/F),
- Plasma concentration at the end of dosing interval ( $C_{\text{trough}}$ )
- The minimum plasma concentration over a 24-hour period at steady state ( $C_{\min}$ )

Additional parameters may be estimated if useful in the interpretation of the data.

**Safety:**

Safety analyses will be carried out using the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug. Analyses will be conducted for Period 1 alone, as well as for Period 1 and Period 2 combined.

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

**Section 1.3 List of Abbreviations and Definition of Terms****Subsection Abbreviations****Delete:**

WOCBP women of childbearing potential

**Section 5.1 Overall Study Design and Plan: Description****Seventh paragraph, last sentence previously read:**

Starting at Week 24 and thereafter, subjects who fail to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits (see Section 5.2.3.1) will be discontinued from the study.

**Has been changed to read:**

Starting at Week 24, at least 20% improvement in BOTH SJC AND TJC compared to baseline is required to remain in the study. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) (see Section 5.2.3.2 for concomitant therapy) must be discontinued from the study.

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

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

**Has been changed to read:**

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission will be conducted.

Study sites and subjects will remain blinded throughout Periods 1 and 2.

**Figure 1. Period 1 Study Design****Figure note previously read:**

- \* The follow-up period is for subjects who do not enter Period 2 or prematurely discontinued study drug and study participation.

**Has been changed to read:**

The follow-up period is for subjects who do not enter Period 2 or prematurely discontinued study drug and study participation.

**Section 5.1 Overall Study Design and Plan: Description****Subsection Screening Period****First paragraph, third and fourth sentence previously read:**

If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure with no additional re-screening possible. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

**Has been changed to read:**

If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Subjects that screen fail for re-tested laboratory values may be re-screened only after consultation with the AbbVie TA MD.

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

**Section 5.1 Overall Study Design and Plan: Description****Subsection Screening Period****Last paragraph, first and second sentence previously read:**

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.

**Has been changed to read:**

Subjects that initially screen fail (for reasons other than re-tested laboratory values) for the study are permitted to re-screen once following re-consent.

**Section 5.1 Overall Study Design and Plan: Description****Subsection Period 1 (12-Week Randomized, Double-Blind Treatment Period)****Add: new last sentence**

Subjects who complete Period 1, but decide not to continue in Period 2 should complete a 30 day follow-up visit after the last dose of study drug.

**Section 5.1 Overall Study Design and Plan: Description****Subsection Period 2 (Blinded Long-Term Extension Period [up to Regulatory Approval of the RA Indication in Japan])**

**Last sentence previously read:**

Starting at Week 24 and thereafter, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits (see Section 5.2.3.2) will be discontinued from the study.

**Has been changed to read:**

Starting at Week 24 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain in the study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24), despite optimization of background RA therapies (see Section 5.2.3.2), must be discontinued from the study.

**Section 5.1 Overall Study Design and Plan: Description****Subsection Premature Discontinuation of Study (Withdrawal of Informed Consent)**

**Last paragraph previously read:**

In addition, if the subject is willing, a 30-day follow-up phone call may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

**Has been changed to read:**

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

**Section 5.2.3.2 Concomitant Therapy**

**Last paragraph, second sentence previously read:**

Initiation of or change in corticosteroids, NSAIDs, acetaminophen, or adding or increasing doses of csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 3) is allowed as per local label.

**Has been changed to read:**

Initiation of or change in corticosteroids, NSAIDs, acetaminophen/paracetamol, low potency analgesics, or csDMARDs (restricted to oral or parenteral MTX, sulfasalazine, leflunomide, bucillamine or iguratimod and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide; see Inclusion Criterion 3) is allowed as per local label.

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

Rifapentine

**Section 5.2.3.3 Prohibited Therapy****Subsection Vaccines****First paragraph****Add: new last sentence**

Live vaccinations are prohibited during the study participation including at least 30 days after the last dose of study drug.

**Section 5.2.3.3 Prohibited Therapy****Subsection Traditional Chinese Medicine****Previously read:**

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

**Has been changed to read:**

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.

**Section 5.2.4 Contraception Recommendations****Subsection Contraception Recommendation for Females****Fifth paragraph, first bullet previously read:**

Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal\*, transdermal\*) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.

**Has been changed to read:**

Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal\*, transdermal\*, injectable\*) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.

**Section 5.2.4 Contraception Recommendations****Subsection Contraception Recommendation for Females****Fifth paragraph, fourth bullet previously read:**

Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.

**Has been changed to read:**

Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the only sexual partner.

**Section 5.2.4 Contraception Recommendations****Subsection Contraception Recommendation for Females****Add: new sixth and seventh paragraph**

If required per local guidelines, 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 and complete documentation is available, contraception measures as defined above are no longer required.

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

It is important to note that contraception and sperm recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib. The concomitant csDMARDs (i.e., methotrexate, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study.

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

As described above, contraception should continue while the subject is on the concomitant csDMARD and that duration of contraception after discontinuation of the csDMARD should be based on the local label.

**Has been changed to read:**

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

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

If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation is available, urine pregnancy test is no longer required.

**Table 2. Study Activities (Period 1)****Table note "o." previously read:**

hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject for all visits except Screening. Investigator should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigator should also refrain from locally testing procalcitonin except for safety evaluations of signs and symptoms of infection management and adverse events. However, results of tests such as hsCRP, serum amyloid A and procalcitonin 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. It should also be noted that any hsCRP, CRP, serial SAA, or serial procalcitonin local tests reported to the Investigator will be recorded as protocol deviations.

**Has been changed to read:**

Central lab hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject for all visits except Screening. Investigator should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigator should also refrain from locally testing procalcitonin except for safety evaluations of signs and symptoms of infection management and adverse events. Results of hsCRP may unblind the treatment assignment and results of tests such as hsCRP, serum amyloid A and procalcitonin 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. Therefore, any local testing of hsCRP or CRP is strongly discouraged. It should also be noted that during Period 1 any hsCRP or CRP, serial SAA, or serial procalcitonin local tests reported to the Investigator will be recorded as protocol deviations.

**Table 2. Study Activities (Period 1)****Table note "r."****Last sentence previously read:**

This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+).

**Has been changed to read:**

This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+) and HBC Ab negative (-). Refer to Section [5.3.1.1](#) Study Procedures Hepatitis Screen for additional details.

**Table 4. Studies Activities (Period 2)**  
**Activity "Chest x-ray"<sup>f</sup> previously read:**

Activity	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks Until Study Completion <sup>a</sup>	Every 24 Weeks Until Study Completion <sup>a</sup>	Every 48 Weeks Until Study Completion <sup>a</sup>	Final/ PD Visit	30-Day F/U Visit <sup>b</sup>
							X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>
Chest x-ray <sup>f</sup>											

**Has been changed to read:**

Activity	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks Until Study Completion <sup>a</sup>	Every 24 Weeks Until Study Completion <sup>a</sup>	Every 48 Weeks Until Study Completion <sup>a</sup>	Final/ PD Visit	30-Day F/U Visit <sup>b</sup>
							X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>
Chest x-ray <sup>f</sup>											

**Table 4. Studies Activities (Period 2)****Table note "f." and "g." previously read:**

- f. Obtain chest x-ray every 48 weeks after Week 48 and PD for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline.
- g. ECGs will be performed every 48 weeks after Week 48 and for subjects who prematurely discontinue from the study. An ECG may be performed at any visit if deemed necessary by the Investigator.

**Has been changed to read:**

- f. Starting at Week 48, obtain chest x-ray every 48 weeks for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline.
- g. Starting at Week 48, ECGs will be performed every 48 weeks and for subjects who prematurely discontinue from the study. An ECG may be performed at any visit if deemed necessary by the Investigator.

**Table 4. Studies Activities (Period 2)****Table note "l."****Add: new last sentence**

If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation is available, urine pregnancy test is no longer required.

**Table 4. Studies Activities (Period 2)****Table note "m."****Add: new last sentence**

If during the course of the study a woman becomes surgically sterile or post-menopausal and complete documentation is available, urine pregnancy test is no longer required.

**Table 4. Studies Activities (Period 2)****Table note "n." previously read:**

hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject. Treatment assignment may be unblinded to Sponsor only when the last subject completes Period 1 (Week 12 visit) for the Week 12 primary analysis for regulatory purposes. Investigator should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigator should also refrain from locally testing procalcitonin

except for safety evaluations of signs and symptoms of infection management and adverse events. However, results of tests such as hsCRP, serum amyloid A and procalcitonin 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. It should also be noted that any hsCRP, CRP, serial SAA, or serial procalcitonin local tests reported to the Investigator will be recorded as protocol deviations.

**Has been changed to read:**

Central lab hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject. Treatment assignment may be unblinded to Sponsor only when the last subject completes Period 1 (Week 12 visit) for the Week 12 primary analysis. Study sites and subjects will remain blinded throughout Periods 1 and 2. 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. Therefore, any local testing of hsCRP or CRP is strongly discouraged.

**Table 4. Studies Activities (Period 2)**

**Table note "q."**

**Delete: second sentence**

The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-DNA is observed.

**Table 4. Studies Activities (Period 2)**

**Table note "q."**

**Last sentence previously read:**

In HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV-DNA PCR test should be performed in every 12 weeks. The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-DNA is observed. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+).

**Has been changed to read:**

This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+) and HBC Ab negative (-). Refer to Section 5.3.1.1 Study Procedures Hepatitis Screen for additional details.

**Section 5.3.1.1 Study Procedures****Subsection TB Testing/TB Prophylaxis****Subheading "Period 1"****Ninth paragraph previously read:**

**Of note: Rifampicin is not allowed for TB prophylaxis.**

**Has been changed to read:**

**Of note: Rifampicin or Rifapentine are not allowed for TB prophylaxis.**

**Section 5.3.1.1 Study Procedures****Subsection TB Testing/TB Prophylaxis****Subheading "Period 2"****Add: new first paragraph**

Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD are not required to repeat either TB test during the study and should be considered positive. The TB risk assessment form will be completed annually for all subjects, regardless of TB test results.

**Section 5.3.1.1 Study Procedures****Subsection TB Testing/TB Prophylaxis****Subheading "Period 2"****Second paragraph previously read:**

If one of the tests has a positive test result (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Expert consultation can be considered per Investigator's discretion.

**Has been changed to read:**

If one of the annual tests has a positive test result (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB.

**Section 5.3.1.1 Study Procedures****Subsection TB Testing/TB Prophylaxis****Subheading "Period 2"****Add: new third, fourth, and fifth paragraph**

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.

Expert consultation for the evaluation/management of TB may be considered per Investigator's discretion.

Any positive TB screen after the patient has started the study, should be reported as an adverse event (AE) of latent TB or active TB (as applicable).

**Section 5.3.1.1 Study Procedures****Subsection TB Testing/TB Prophylaxis****Subheading "Period 2"****Third paragraph previously read:**

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

**Has been changed to read:**

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

**Section 5.3.1.1 Study Procedures****Subsection TB Testing/TB Prophylaxis****Subheading "Period 2"****Fourth paragraph previously read:**

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

**Has been changed to read:**

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

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

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

Annually and at PD for subjects with TB risk factors as identified by the TB risk assessment form (Appendix E), or for subjects living in areas endemic for TB or for subjects with newly positive PPD and/or QuantiFERON<sup>®</sup>-TB Gold test.

**Has been changed to read:**

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

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

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

**Has been changed to read:**

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

**Section 5.3.1.1 Study Procedures****Subsection 12-Lead ECG****First paragraph, fourth sentence previously read:**

In these cases, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well.

**Has been changed to read:**

A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. In case of QTcF prolongation, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well.

**Section 5.3.1.1 Study Procedures****Subsection Pregnancy Test****Second paragraph, last bullet previously read:**

If a urine pregnancy test post-baseline is positive, study drug needs to be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be permanently discontinued.

**Has been changed to read:**

If a urine pregnancy test post-baseline is positive, study drug needs to be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative,

study drug may be resumed. 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 ( $\geq 3$  days later) to document continued lack of a positive result.

#### **Section 5.3.1.1 Study Procedures**

##### **Subsection Pregnancy Test**

**Add: new fifth paragraph**

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.

#### **Table 5. Clinical Laboratory Tests**

**Column "Clinical Chemistry<sup>a</sup> (Central Lab)," test "INR (reflex only)<sup>c</sup>" previously read:**

INR (reflex only)<sup>c</sup>

**Has been changed to read:**

INR<sup>c</sup>

#### **Table 5. Clinical Laboratory Tests**

**Table note "c." previously read:**

INR will be measured if ALT and/or AST  $> 3 \times$  ULN.

**Has been changed to read:**

INR will be measured with a separate blood sample if ALT and/or AST  $> 3 \times$  ULN.

#### **Table 5. Clinical Laboratory Tests**

**Table note "e." previously read:**

At Screening only. In case of HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV-DNA PCR test should be performed every 12 weeks. The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-

DNA is observed. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+).

**Has been changed to read:**

In case of HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV-DNA PCR test should be performed every 12 weeks. HBV-DNA PCR testing every 12 weeks is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+) and HBc Ab negative (-).

HBV DNA testing is also required for subjects who meet specific toxicity management criteria (See ALT/AST toxicity management criteria in [Table 7](#)).

**Table 5. Clinical Laboratory Tests**

**Table note "h." previously read:**

The hsCRP results starting from baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, and the subject.

**Has been changed to read:**

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 be blunted in subjects taking a JAK inhibitor, thereby limiting its clinical utility in the setting of a possible safety assessment or adverse event management. 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.

**Table 5. Clinical Laboratory Tests**

**Table note "l." previously read:**

A urine pregnancy test will be performed for all women of childbearing potential at the Baseline Visit prior to the first dose of study drug and all subsequent visits except Week 1. If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is

positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required. If a urine pregnancy test 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.

**Has been changed to read:**

A urine pregnancy test will be performed for all women of childbearing potential at the Baseline Visit prior to the first dose of study drug and all subsequent visits except Week 1. In Period 2, for women of childbearing potential, a urine pregnancy test will be performed at all visits, including the 30 days follow-up visit, and starting at Week 24 a urine pregnancy test will be performed monthly at home between scheduled study visits. 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 started or resumed. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required ( $\geq 3$  days later) to document continued lack of a positive result. 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.

**Section 5.3.1.1 Study Procedures****Subsection Hepatitis Screen****Heading "Hepatitis B:"****First paragraph, first and second bullet previously read:**

- HBs Ag
- HBc Ab/anti-HBc

**Has been changed to read:**

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

**Section 5.3.1.1 Study Procedures****Subsection Hepatitis Screen****Subheading "Hepatitis B:"****Third paragraph, last sub bullet previously read:**

In case HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV DNA PCR test should be performed every 12 weeks. The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-DNA is observed. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+).

**Has been changed to read:**

- For subjects with HBs Ab positive (+) and/or HBc Ab positive (+) and negative HBV DNA at screening, HBV DNA PCR test should be performed every 12 weeks. HBV-DNA PCR testing every 12 weeks is not necessary in case of patients with history of HBV vaccine and HBs Ab positive (+) and HBc Ab negative (-).
- Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop a positive result for HBV DNA PCR testing during the study accompanied by the following should be referred to a hepatologist within 1 week for consultation and recommendation

regarding subsequent treatment, and study drug interruption should be considered per local guidelines:

- an ALT  $> 5 \times$  ULN OR
- ALT or AST  $> 3 \times$  ULN and either a total bilirubin  $> 2 \times$  ULN or INR  $> 1.5$  OR
- ALT or AST  $> 3 \times$  ULN along with clinical signs of possible hepatitis.

#### **Section 5.3.2.1 Collection of Samples for Analysis**

**Last bullet previously read:**

During one of the study visits, including unscheduled visits occurring after Week 1, in Period 1 or Period 2 excluding Baseline and Premature Discontinuation visit prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose in 32 subjects who participate in the intensive pharmacokinetic study.

**Has been changed to read:**

During one of the study visits, including unscheduled visits occurring after Week 1, in Period 1 or Period 2 excluding Baseline and Premature Discontinuation visit prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose in approximately 32 subjects who participate in the intensive pharmacokinetic study.

#### **Section 5.3.2.1 Collection of Samples for Analysis**

**Third paragraph, first sentence previously read:**

Subjects who participate in the intensive pharmacokinetic assessment (32 subjects) should be fasting for at least 8 hours prior to drug administration and will not take the study drug until after collection of the pre-dose blood sample during the study visit chosen for intensive PK assessment.

**Has been changed to read:**

Subjects who participate in the intensive pharmacokinetic assessment (approximately 32 subjects) should be fasting for at least 8 hours prior to drug administration and will not

take the study drug until after collection of the pre-dose blood sample during the study visit chosen for intensive PK assessment.

**Section 5.3.3.1.2 Key Secondary Variables****First paragraph previously read:**

Key secondary endpoints at Week 12 are:

**Has been changed to read:**

Key secondary endpoints at Week 12 (if not otherwise indicated) are:

**Section 5.3.3.1.3 Additional Variables****Last bullet list****Add: new third and fourth bullet**

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

**Section 5.4.1 Discontinuation of Individual Subjects****Twelfth and thirteenth bullet previously read:**

- If the subject experiences a study drug interruption > 7 consecutive days during Weeks 1 through 24 or > 30 consecutive days after Week 24 (other than for reasons listed in Section 6.1.7).
- Starting at Week 24 and thereafter, subjects who fail to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits.

**Has been changed to read:**

Starting at Week 24, at least 20% improvement in BOTH TJC and SJC compared to baseline is required to remain in the study. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 24) must be discontinued from the study.

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**Section 5.4.1 Discontinuation of Individual Subjects****Third paragraph, second sentence previously read:**

A 30-day follow-up phone call may occur for subjects who prematurely discontinued from study drug and study participation to determine the status of any ABT-494 ongoing AEs/SAEs or the occurrence of any new AEs/SAEs (refer to Section 5.1 regarding Follow-Up Visit).

**Has been changed to read:**

A 30-day follow-up visit/phone call may occur for subjects who prematurely discontinued from study drug and study participation to determine the status of any upadacitinib ongoing AEs/SAEs or the occurrence of any new AEs/SAEs (refer to Section 5.1 regarding Follow-Up Visit).

**Table 6. Identity of Investigational Product****Investigational Product "Upadacitinib"****Column "Formulation" previously read:**

Tablet

**Has been changed to read:**

Tablet (extended-release)

**Section 5.5.5.1 Blinding of Investigational Product****Last paragraph previously read:**

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

**Has been changed to read:**

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission

will be conducted. Study sites and subjects will remain blinded for the duration of the study.

#### **Section 6.1.1.3 Adverse Events of Special Interest**

**Bulleted list previously read:**

- Serious infections, opportunistic infections, herpes zoster, and TB;
- Malignancy and lymphoproliferative disorders;
- Gastrointestinal perforations;
- Cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Lipid profile changes;
- Anemia and hemoglobin effects;
- Decreased neutrophil counts;
- Decreased lymphocyte counts;
- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Increased creatine phosphokinase (CPK).

**Has been changed to read:**

- Serious infections
- Opportunistic infections
- Herpes zoster
- Tuberculosis;
- Malignancy (all types);
- Gastrointestinal perforations;
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Lipid profile changes;
- Anemia;
- Neutropenia;
- Lymphopenia;

- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Elevated creatine phosphokinase (CPK);
- Embolic and thrombotic events (non-cardiac, non-CNS).

**Section 6.1.3 Relationship to Study Drug**

"Reasonable Possibility" and "No Reasonable Possibility" previously read:

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

**Has been changed to read:**

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

**Section 6.1.3 Relationship to Study Drug**

**Second paragraph, first sentence previously read:**

For relationship assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated."

**Has been changed to read:**

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated."

**Section 6.1.4 Adverse Event Collection Period****Last paragraph****Add: new last bullet**

Emolic and thrombotic events (non-cardiac, non-CNS).

**Section 6.1.5 Serious Adverse Event Reporting****"Primary Therapeutic Area Medical Director:" previously read:**

AbbVie Inc.

[REDACTED] 1500 Seaport Blvd.  
Redwood City, CA 94063**Contact Information:**

Office: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

**Has been changed to read:**AbbVie Deutschland GmbH & Co. KG  
Knollstrasse – [REDACTED]  
67061 Ludwigshafen  
Germany**Contact Information:**

Office: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

**Section 6.1.5 Serious Adverse Event Reporting****"Secondary Contact (Regional Medical Monitor):"****"Telephone Contact Information:" previously read:**

Telephone Contact Information:

**Has been changed to read:**

Contact Information:

**Section 6.1.5 Serious Adverse Event Reporting****Seventh paragraph, first sentence previously read:**

The Sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

**Has been changed to read:**

The Sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Global and Local Regulations.

**Section 6.1.7 Toxicity Management****Second paragraph****Delete: sixth sentence**

If study drug has been interrupted for a serious infection for more than 7 consecutive days during the first 24 weeks of the study or 30 consecutive days thereafter, the subject must be discontinued from the study.

**Section 6.1.7 Toxicity Management****Sixth paragraph previously read:**

**ECG Abnormality:** Subjects must be discontinued for an ECG change considered clinically significant OR a confirmed absolute QTcF value > 500 msec.

**Has been changed to read:**

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

**Section 6.1.7 Toxicity Management****Seventh paragraph****Add: new third and fourth sentence**

All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per [Table 7](#), the repeat testing must occur as soon as possible.

**Table 7. Specific Toxicity Management Guidelines for Abnormal Laboratory Values Laboratory Parameter "AST or ALT," "Serum Creatinine," and "Creatine Phosphokinase" previously read:**

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	<ul style="list-style-type: none"><li>Discontinue study drug if confirmed ALT or AST <math>&gt; 3 \times</math> ULN and total bilirubin <math>&gt; 2 \times</math> ULN (repeat testing with new samples are required for both) or confirmed ALT or AST <math>&gt; 3 \times</math> ULN with new sample and an abnormal international normalized ratio (INR) <math>&gt; 1.5</math>.</li><li>INR will be measured every time subjects have ALT or AST <math>&gt; 3 \times</math> ULN by the central lab by reflex testing</li><li>Discontinue study drug if confirmed ALT or AST <math>&gt; 3 \times</math> 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 (<math>&gt; 5\%</math>).</li><li>Discontinue study drug if confirmed ALT or AST <math>&gt; 8 \times</math> ULN by repeat testing with new sample.</li><li>Discontinue study drug if confirmed ALT or AST <math>&gt; 5 \times</math> ULN by repeat testing with new sample for more than 2 weeks.</li></ul> Complete supplemental hepatic eCRF.
Serum Creatinine	<ul style="list-style-type: none"><li>Change from baseline <math>&gt; 1.5 \times</math> of serum creatinine baseline value. If confirmed the change from baseline <math>&gt; 1.5</math>-fold by repeat testing with new sample, interrupt study drug dosing until serum creatinine value returns to <math>\leq 1.5</math>-fold baseline value.</li><li>If serum creatinine <math>\geq 2</math> mg/dL, first interrupt study drug, then contact AbbVie TA MD. Repeat test and re-start study drug once serum creatinine returns to normal reference range or its baseline value.</li></ul> Complete supplemental renal eCRF.
Creatine Phosphokinase	<ul style="list-style-type: none"><li>For any CPK value <math>\geq 4 \times</math> ULN, a supplemental CPK eCRF should be completed. Subjects may continue on study drug.</li><li>If CPK <math>\geq 4 \times</math> ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD.</li></ul>

**Has been changed to read:**

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	<ul style="list-style-type: none"><li>Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 3 \times</math> ULN by repeat testing with new sample and either a total bilirubin <math>&gt; 2 \times</math> ULN or an international normalized ratio (INR) <math>&gt; 1.5</math>.<ul style="list-style-type: none"><li>INR will be measured with a separate blood sample every time subjects have ALT or AST <math>&gt; 3 \times</math> ULN by the central lab. A repeat test of INR is not needed for determination if above toxicity management criteria are met.</li></ul></li><li>Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 3 \times</math> 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 (<math>&gt; 5\%</math>).</li><li>Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 5 \times</math> ULN by repeat testing with new sample for more than 2 weeks.</li><li>Interrupt study drug immediately if confirmed ALT or AST <math>&gt; 8 \times</math> ULN by repeat testing with new sample.</li><li>Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found.</li></ul> <p>For any confirmed ALT or AST elevations <math>&gt; 3</math> ULN, complete supplemental hepatic eCRF.</p> <ul style="list-style-type: none"><li>Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within 1 week:<ul style="list-style-type: none"><li>ALT <math>&gt; 5 \times</math> ULN OR</li><li>ALT or AST <math>&gt; 3 \times</math> ULN and either a total bilirubin <math>&gt; 2 \times</math> ULN or INR <math>&gt; 1.5</math> OR</li><li>ALT or AST <math>&gt; 3 \times</math> ULN along with clinical signs of possible hepatitis.</li></ul></li></ul> <p>Subjects who develop a positive result for HBV DNA PCR testing should be referred to a hepatologist within 1 week for consultation and recommendation regarding subsequent treatment, and study drug interruption should be considered per local guidelines.</p>

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	<ul style="list-style-type: none"><li>• If serum creatine is <math>&gt; 1.5 \times</math> the baseline value and <math>&gt; \text{ULN}</math>, 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 <math>\leq 1.5 \times</math> baseline value and <math>\leq \text{ULN}</math>.</li><li>• If confirmed serum creatinine <math>\geq 2 \text{ mg/dL}</math>, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value.</li></ul> <p>For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.</p>
Creatine Phosphokinase	<ul style="list-style-type: none"><li>• If confirmed CPK value <math>\geq 4 \times \text{ULN}</math> and there are no symptoms suggestive of myositis or rhabdomyolysis, the subject may continue study drug at the investigator's discretion.</li><li>• If CPK <math>\geq 4 \times \text{ULN}</math> accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD.</li></ul> <p>For the above CPK elevation scenarios, complete supplemental CPK eCRF.</p>

### Section 6.2.2 Reporting

**First paragraph, first sentence previously read:**

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form.

**Has been changed to read:**

Product Complaints concerning the investigational product must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form.

**Section 7.0 Protocol Deviations****Contact information previously read:**

Primary Contact:



AbbVie Srl  
S.R. Pontina Km 52 snc  
04011 Campoverde (LT)  
ITALY

Office: [REDACTED]  
Fax: [REDACTED]  
Email: [REDACTED]

Alternate Contact:



United States

Office: [REDACTED]  
Fax: [REDACTED]  
Email: [REDACTED]

**Has been changed to read:**

Primary Contact:



AbbVie Srl  
Viale dell'Arte, 25  
00144 Roma  
Italy

Office: [REDACTED]  
Fax: [REDACTED]  
Email: [REDACTED]

Alternate Contact:



United States

Office: [REDACTED]  
Fax: [REDACTED]  
Email: [REDACTED]

**Section 8.1 Statistical and Analytical Plans****First paragraph, first sentence previously read:**

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) for the purpose of regulatory submission.

**Has been changed to read:**

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12) and additional unblinded analyses for the purpose of regulatory submission will be conducted.

**Section 8.1.4.1.5 Imputation Methods****Fourth paragraph, last sentence previously read:**

In NRI analysis, subjects who prematurely discontinue the study drug will be considered non-responders after discontinuation.

**Has been changed to read:**

In NRI analysis, subjects who prematurely discontinue the study drug will be considered non-responders on or after discontinuation date.

**Section 8.1.4.2 Long-Term Efficacy Analysis for Period 1 and Period 2 Combined**  
**Delete: last paragraph**

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.

**Section 8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)****Fifth and sixth bullet previously read:**

- Frequent AEs (reported in 2% of subjects or more in any treatment group);
- Frequent reasonably possibly related AEs (reported in 2% of subjects or more in any treatment group);

**Has been changed to read:**

- Frequent AEs (reported in 5% of subjects or more in any treatment group);
- Frequent reasonably possibly related AEs (reported in 5% of subjects or more in any treatment group);

**Section 8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)****Seventh paragraph previously read:**

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

**Has been changed to read:**

The AEs of special interest (including but not limited to serious infection, opportunistic infection, malignancy, non-melanoma skin cancer (NMSC), malignancy other than NMSC, lymphoma, hepatic disorder, gastrointestinal perforation, anemia, neutropenia, lymphopenia, herpes zoster, increased CPK, renal dysfunction, tuberculosis, adjudicated cardiovascular events and embolic and thrombotic events (non-cardiac, non-CNS) 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.

**Section 8.1.5.3 Analysis of Laboratory, Vital Sign, and ECG Data****Third paragraph previously read:**

The laboratory data will be categorized as low, normal, or high based on the normal ranges of the laboratory used in this study. The shift tables will tabulate the number and percentage of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range. Shift tables for liver elevations from baseline to post-baseline maximum value will be summarized for each treatment group.

**Has been changed to read:**

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

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

## Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
		Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacokinetics and Pharmacodynamics
		Bioanalysis
		Clinical Program Development
		Global Drug Supply Management
		Japan Development
		Japan Development

Has been changed to read:

Name	Title	Functional Area
		Therapeutic Area
		Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Clinical Pharmacokinetics and Pharmacodynamics
		Bioanalysis
		Clinical Program Development
		Japan Development
		Japan Development

**Appendix N. Rheumatology Common Toxicity Criteria v.2.0 Example****Subsection L. Chemistry****"L9." and "L11." previously read:**

L9. CPK (also if polymyositis-disease)

L11. Creatinine (mg/dL)

**Has been changed to read:**

L9. CPK (also if polymyositis-disease)\*

L11. Creatinine (mg/dL)\*

**Appendix N. Rheumatology Common Toxicity Criteria v.2.0 Example****Add: new table note "/\*"**

- \* For CPK and Creatinine NCI CTC grading will be used. For CPK therefore the following gradings apply: Grade 1:  $> \text{ULN} - 2.5 \times \text{ULN}$ ; Grade 2:  $> 2.5 - 5.0 \times \text{ULN}$ ; Grade 3:  $> 5.0 - 10.0 \times \text{ULN}$ ; Grade 4:  $> 10.0 \times \text{ULN}$ ; For Creatinine the following gradings apply: Grade 1:  $> 1 - 1.5 \times \text{Baseline}$ ;  $> \text{ULN} - 1.5 \times \text{ULN}$ ; Grade 2:  $> 1.5 - 3.0 \times \text{ULN}$ ; Grade 3:  $> 3.0 \times \text{Baseline}$ ;  $> 3.0 - 6.0 \times \text{ULN}$ ; Grade 4:  $> 6.0 \times \text{ULN}$

## Document Approval

Study M14663 - A Phase 2b/3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti?Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs - Amendment 5 - 23Feb2018

Version: 1.0

Date: 05-Mar-2018 08:42:20 PM Company ID: 03052018-00F9F683C1B006-00001-en

Signed by:	Date:	Meaning Of Signature:
	23-Feb-2018 03:42:11 PM	Approver
	23-Feb-2018 05:49:28 PM	Approver
	23-Feb-2018 06:02:54 PM	Approver
	24-Feb-2018 11:28:58 PM	Approver
	25-Feb-2018 11:23:11 AM	Approver
	26-Feb-2018 10:05:49 AM	Approver
	26-Feb-2018 02:20:04 PM	Approver
	26-Feb-2018 03:54:31 PM	Approver
	05-Mar-2018 08:42:19 PM	Approver