1.0 Title Page

Clinical Study Protocol M15-554

A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – *SELECT – PsA 2*

Incorporating Administrative Changes 1, 2 and Amendments 1, 2, 2.01 (VHP Countries), 3, 4, 5, 6, 7 and 8 (All Countries except Belgium, Czech Republic, France, Greece, Hungary, Japan, New Zealand, and Portugal)

AbbVie Investigational Product:	Upadacitinib
Date:	29 January 2021
Development Phase:	3
Study Design:	A Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study
EudraCT Number:	2016-004152-30
Investigators	Multicenter trial (Investigator information is on file at AbbVie)
Sponsor:	**For Non-EU Countries:** AbbVie Inc.* 1 North Waukegan Road [redacted] North Chicago, IL 60064 United States of America **For EU Countries:** AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany

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

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	10 February 2017
Amendment 1	27 February 2017
Amendment 2	03 March 2017
Administrative Change 1	19 May 2017
Amendment 2.01 (VHP Countries)	21 June 2017
Amendment 3	07 July 2017
Amendment 4	23 March 2018
Administrative Change 2	15 November 2018
Amendment 5	14 January 2019
Amendment 6	04 October 2019
Amendment 7	01 April 2020
Amendment 7.01 (Belgium, Czech Republic, France, Greece, Hungary, Japan, New Zealand, and Portugal Only)	23 July 2020
Administrative Change 3 (JP Only)	01 September 2020
Amendment 7.01.01 (JP Only)	23 November 2020

The purpose of this amendment is to:

- Apply administrative changes throughout protocol

  Rationale: *Revised text to improve consistency and readability, and/or provide clarification.*
- Apply updates throughout applicable sections of the protocol to add the generic name "upadacitinib" in place of "ABT-494."

  Rationale: *To update study drug name to the appropriate generic name.*
- Apply updates throughout applicable sections of the protocol to switch all subjects currently on upadacitinib 30 mg QD to upadacitinib 15 mg QD in Period 2 upon approval of this protocol amendment, to occur at each subject's next scheduled study visit.

Rationale: *The dose of 15 mg QD of upadacitinib has been determined to be the optimal dose for patients with active psoriatic arthritis (PsA) and it is the proposed dose for marketing authorization globally.*

- Update Section 5.1 Overall Study Design and Plan: Description, Discontinuation of Study Drug and Continuation of Study Participation (Period 1 and Period 2); Premature Discontinuation of Study (Withdrawal of Informed Consent) (Period 1 and Period 2), to clarify that subjects should complete a discontinuation visit preferably prior to initiation of another therapy.

  Rationale: *Initiation/addition of another therapy prior to the discontinuation visit may confound measurements and assessments taken at the discontinuation visit.*

- Update Section 5.3.1.1 Study Procedures, Vital Signs, Weight, and Height to add subject visits may be conducted via phone or video conference and that vital signs and weight may be performed by the subject or caregiver as needed.

  Rationale: *To provide flexibility in conduct of study visits and timing of certain study procedures during state of emergency/pandemic times.*

- Update Section 5.3.1.1 Study Procedures, Physical Exam and Chest X-Ray (CXR) to add that these assessment(s) will be performed at the next feasible visit if scheduled study visit cannot be conducted due to a state of emergency or pandemic.

  Rationale: *To provide flexibility in conduct of study visits and timing of certain study procedures during state of emergency/pandemic times.*

- Update Section 5.3.1.1 Study Procedures, TB Testing/TB Prophylaxis to clarify how subjects should respond to questions on the TB risk assessment form at time of annual evaluation.

  Rationale: *To ensure consistent responses throughout the study and prevent unnecessary chest x-rays in subjects at low risk for TB.*

- Update Section 5.3.1.1 Study Procedures, TB Testing/TB Prophylaxis to add if a subject has seroconversion on an annual TB test but does not have any TB risk factors, if CXR cannot be done due to state of emergency or pandemic situations, CXR should be performed as soon as possible and investigator

should contact AbbVie TA MD to determine if study drug should be continued.

Rationale: *To provide flexibility during state of emergency/pandemic times for CXR requirement for subjects with seroconversion on annual TB test.*

- Update Section 5.3.1.1 Study Procedures, Clinical Laboratory Tests to add the use of local laboratories during state of emergency/pandemic times to monitor safety.

  Rationale: *To provide flexibility during state of emergency/pandemic times to help study sites manage subject safety.*

- Update Section 5.3.1.1 Study Procedures, Study Drug Dispensing, Dosing, and Compliance to add direct to patient (DTP) study drug shipment.

  Rationale: *To provide flexibility during state of emergency/pandemic times to help study sites manage subject continued use of study drug when appropriate.*

- Update Section 5.3.1.1 Study Procedures, Patient Questionnaires; and Section 10.2 Case Report Forms, Electronic Patient Reported to add telephone interview for PRO collection.

  Rationale: *To provide flexibility during state of emergency/pandemic times to collect PRO data.*

- Update Section 5.4.1 Discontinuation of Individual Subjects, text added to 11th bullet and Section 6.1.7 Toxicity Management to clarify definition of gastrointestinal perforation.

  Rationale: *To clarify the definition of gastrointestinal perforation to be an acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention.*

- Update Section 6.1.5 Serious Adverse Event and Malignancy Reporting to update address and telephone number.

  Rationale: *Global address and telephone number were changed.*

- Update Section 6.1.7 Toxicity Management to add guidelines for interruption of study drug in subjects with signs and/or symptoms or suspicion of COVID-19 infection.

  Rationale: *To provide guidance on study drug interruption for subjects with confirmed diagnosis of COVID-19 infection and subjects with signs and/or*

symptoms and suspicion of COVID-19 infection and the necessity of COVID-19 eCRF completion.

- Update Section 6.1.7 Toxicity Management, Table 4 Specific Toxicity Management Guidelines for Abnormal Laboratory Values to update AST/ALT laboratory toxicity management guidelines.

  Rationale: *To update AST/ALT laboratory toxicity management guidelines for ALT or AST > 8 × ULN.*

- Update Section 8.1 Statistical and Analytical Plans to add the handling of change in dose analysis will be described in the Statistical Analysis Plan.

  Rationale: *Because of the dose change, analysis will be updated. The details will be described in the Statistical Analysis Plan (SAP).*

- Update Section 9.2 Ethical Conduct of the Study to add situations leading to difficulties in performing protocol-specific procedures.

  Rationale: *To provide flexibility during state of emergency/pandemic times for alternative measures which must be allowed by local regulations and permitted by IRB/IEC.*

- Update Section 9.3 Subject Information and Consent to add additional verbal consent in the informed consent process if required prior to adaptations or substantial changes in study conduct resulting from state-of emergency or pandemic situations.

  Rationale: *In addition to the study informed consent, additional verbal consent may be required from the subject for adaptions in study conduct needed during state-of-emergency or pandemic situation.*

- Update Section 10.1 Source Documents to add remote monitoring data may be employed.

  Rationale: *To provide flexibility during state of emergency/pandemic times to allow remote monitoring of data.*

- Update Section 10.2 Case Report Forms to add that supplemental case report forms should be completed in the event of COVID-19 (coronavirus SARS-CoV-2) related missing/incomplete/virtual visits, study drug interruptions or discontinuations or adverse events (including capture of specific signs/symptoms of infection and testing results).

Rationale: *Information specific to study-related effects of COVID-19 (coronavirus SARS-CoV-2) will be collected.*

- Update Section 10.2 Case Report Forms, Electronic Patient Reported Data to update vendor name.

  Rationale: *To update vendor name from CRF Health to Signant Health.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Updated list of Protocol Signatories responsible for Amendment 8.0.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-554
Name of Study Drug: upadacitinib (ABT-494)	**Phase of Development:** 3
Name of Active Ingredient: upadacitinib	**Date of Protocol Synopsis:** 29 January 2021
Protocol Title: A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – *SELECT – PsA 2*	
Objectives: Period 1 1. To compare the efficacy of upadacitinib 15 mg once daily (QD) and 30 mg QD versus placebo for the treatment of signs and symptoms in subjects with moderately to severely active Psoriatic Arthritis (PsA) who have an inadequate response to bDMARDs (Bio-IR). 2. To compare the safety and tolerability of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have an inadequate response to bDMARDs. Period 2 To evaluate the long-term safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	
Investigators: Multicenter	
Study Sites: Approximately 165 sites	
Study Population: Patients with active PsA despite prior use of at least one bDMARD.	
Number of Subjects to be Enrolled: Approximately 630	
Methodology: This is a Phase 3 multicenter study that includes two periods. Period 1 is 56-weeks in duration and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have an inadequate response to bDMARDs (Bio-IR). Period 2 is an open-label (blinded until the last subject completes the last visit of Period 1), long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1. The study is designed to enroll approximately 630 subjects at approximately 165 study centers worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. The study duration will include a 35-day screening period; a 56-week blinded period which includes 24 weeks of double-blind, placebo-controlled treatment followed by 32 weeks of treatment blinded to the dose of upadacitinib (Period 1); a long-term extension period of up to a total treatment duration of approximately 3 years ([blinded until the last subject completes the last visit of Period 1] Period 2); and a 30-day follow-up call or visit.	

Methodology (Continued):

Subjects who meet eligibility criteria will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, and number of prior failed (had an inadequate response to) biologic DMARDs (1 vs > 1), except for subjects from Japan, for which randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA) only, and then will be randomized in a 2:2:1:1 ratio to one of four treatment groups:

Group 1: upadacitinib 15 mg QD (N = 210)

Group 2: upadacitinib 30 mg QD (N = 210)

Group 3: Placebo followed by upadacitinib 15 mg QD (N = 105)

Group 4: Placebo followed by upadacitinib 30 mg QD (N = 105)

No more than approximately 40% of subjects will be enrolled with < 3% BSA extent of psoriasis and no more than approximately 30% of subjects will be enrolled with prior failure of more than 1 biologic DMARD.

Subjects will receive oral study drug QD (upadacitinib 15 mg, upadacitinib 30 mg, or matching placebo) until the end of the study or they discontinue study drug.

Subjects who were assigned to placebo at baseline will be preassigned to receiving either upadacitinib 15 mg QD or upadacitinib 30 mg QD starting at Week 24 in a 1:1 ratio. Subjects who complete the Week 56 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (total study duration up to approximately 3 years). Subjects will continue study treatment as assigned in Period 1. Subjects will continue to receive upadacitinib 15 mg QD or upadacitinib 30 mg QD, respectively, in a blinded manner until the last subject completes the last visit of Period 1 (Week 56), when study drug assignment in both periods will be unblinded to the sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Subjects must have had inadequate response to ≥ 1 bDMARD prior to the Screening visit and must have discontinued all bDMARDs prior to the first dose of study drug. No background non-biologic DMARD therapy is required during participation in this study. For subjects who are on non-biologic DMARD therapy at baseline (methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), apremilast, hydroxychloroquine (HCQ), bucillamine or iguratimod), non-biologic DMARDs should have been started ≥ 12 weeks prior to the baseline visit, must be at stable dose for ≥ 4 weeks prior to the first dose of study drug and remain at stable dose through Week 36 of the study; the non-biologic DMARD dose may be decreased only for safety reasons. In addition, all subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Please refer to Sections 5.2.3.1 and 5.2.3.2 for additional details related to prior and concomitant DMARD therapy, respectively. Starting at the Week 36 visit (after Week 36 assessments have been performed), initiation of or change in background PsA medication(s) including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, low potency opiates, and non-biologic DMARDs (concomitant use of up to 2 non-biologic DMARDs except the combination of MTX and leflunomide), is allowed as per local label with maximum doses as outlined in Section 5.2.3.3.

At Week 16, subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) will add or modify background therapy for PsA.

At Week 24, all subjects allocated to placebo at Baseline will be switched to blinded upadacitinib (randomized at baseline to either 15 mg QD or 30 mg QD) treatment regardless of clinical response.

Methodology (Continued):

After the last subject completes Week 24 study visit, an unblinded analysis will be conducted for the purpose of initial regulatory submission. To maintain integrity of the trial during the blinded 56-week period, study sites and subjects will remain blinded until all subjects have reached Week 56. A second unblinded analysis may be conducted for regulatory purposes after all subjects have completed Period 1. A final analysis will be conducted after all subjects have completed Period 2.

Starting at Week 36, subjects who fail to demonstrate at least 20% improvement in either or both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, at least ≥ 18 years old at Screening
2. Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR) criteria
3. Subject has active disease at Baseline defined as ≥ 3 tender joints (based on 68 joint counts) and ≥ 3 swollen joints (based on 66 joint counts) at Screening and Baseline Visits
4. Diagnosis of active plaque psoriasis or documented history of plaque psoriasis
5. Subject has had an inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to treatment with at least 1 bDMARD

Main Exclusion:

1. Prior exposure to any Janus Kinase (JAK) inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, and filgotinib)
2. Current treatment with > 2 non-biologic DMARDs or use of DMARDs other than MTX, SSZ, LEF, apremilast, HCQ, bucillamine or iguratimod or use of MTX in combination with LEF at Baseline
3. History of fibromyalgia, any arthritis with onset prior to age 17 years, or current diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, systemic lupus erythematosus). Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made. Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly.

Investigational Product:	Upadacitinib (ABT-494)
Doses:	15 mg, or 30 mg once daily
Mode of Administration:	Oral
Reference Therapy:	Matching placebo for upadacitinib (ABT-494)
Dose:	1 tablet once daily
Mode of Administration:	Oral

Duration of Treatment: 152 weeks

Criteria for Evaluation:

Efficacy:

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

The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo) are:

1. Change from baseline in HAQ-DI at Week 12;
2. Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16;
3. Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline);
4. Change from baseline in SF-36 PCS at Week 12;
5. Change from baseline in FACIT-Fatigue Questionnaire at Week 12;
6. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
7. Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16.

Additional key secondary efficacy endpoints (each dose of upadacitinib versus placebo) are:

- ACR50/70 response at Week 12;
- ACR20 response at Week 2.

ACR20/50/70 response rates will be determined based on 20%/50%/70% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain NRS, PtGA of Disease Activity NRS, PGA of Disease Activity NRS, HAQ-DI, or hs CRP.

The proportion of subjects achieving MDA will be determined based on subjects fulfilling 5 of 7 outcome measures: TJC ≤ 1; SJC ≤ 1; PASI ≤ 1 or BSA-Ps ≤ 3%; patient assessment of pain ≤ 1.5 (0 – 10 NRS); PtGA-disease activity ≤ 2 (0 – 10 NRS); HAQ-DI score ≤ 0.5; and tender entheseal points ≤ 1.

The following outcome measures will be assessed at scheduled time points other than those specified for the primary and key secondary variables:

- Change from baseline in individual components of ACR response;
  - Change from baseline in Tender Joint Count (TJC) (0 – 68);
  - Change from baseline in Swollen Joint Count (SJC) (0 – 66);
  - Change from baseline in Physician Global Assessment (PGA) – Disease Activity;
  - Change from baseline in Patient's Global Assessment (PtGA) – Disease Activity;
  - Change from baseline in Patient's Assessment of Pain Numerical Rating Scale (NRS);
  - Change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI);
  - Change from baseline in High-Sensitivity C Reactive Protein (hs-CRP);
- ACR 20/50/70 response rates;
- Change from baseline in Leeds Dactylitis Index (LDI);
- Change from baseline in dactylitis count;
- Proportion of subjects with resolution of dactylitis;
- Change from baseline in LEI;
- Proportion of subjects with resolution of enthesitis sites included in the LEI;

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Change from baseline in SPARCC Enthesitis Index;
- Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index;
- Change from baseline in total enthesitis count;
- Proportion of subjects with resolution of enthesitis;
- PASI 75/90/100 response rates (for subjects with ≥ 3% Body Surface Area (BSA) psoriasis at baseline);
- Proportion of subjects achieving a static Investigator Global Assessment of psoriasis (sIGA) score of 0 or 1 and at least a 2-point improvement from baseline;
- BSA-Ps;
- Modified Psoriatic Arthritis Response Criteria (PsARC) response rate;
- Change from baseline in Disease Activity Score 28 (DAS28) (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in PsA Disease Activity Score (PASDAS);
- Change from baseline in Disease Activity In Psoriatic Arthritis (DAPSA) score;
- Change from baseline in Short Form 36 (SF-36) Health Questionnaire;
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire;
- Change from baseline in EuroQol-5D-5L (EQ-5D-5L) Questionnaire;
- Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire;
- Health Resource Utilization (HRU);
- Proportion of subjects achieving MDA;
- Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire;
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);
- BASDAI 50 response rates;
- Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6);
- Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS);
- Proportion of subjects with ASDAS Inactive Disease;
- Proportion of subjects with ASDAS Major Improvement;
- Proportion of subjects with ASDAS Clinically Important Improvement;
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35).

Criteria for Evaluation (Continued):

Pharmacokinetic:

Blood samples for assay of upadacitinib and possibly other medications in plasma will be collected at each visit after baseline in Period 1.

Exploratory Research Variables and Validation Studies (Optional):

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

Safety:

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

Statistical Methods:

Efficacy:

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

Period 1 Efficacy

Analysis of the Primary and Key Secondary Endpoints:

For the global analysis, comparisons of the primary and key secondary efficacy endpoints will be made between the upadacitinib 15 mg QD and 30 mg QD groups versus the combined placebo groups for all subjects. The overall type I error rate of the primary and key secondary endpoints for the two doses will be strongly controlled using a graphical multiple testing procedure.

For binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparisons for each of the upadacitinib treatment groups to 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 for each of the upadacitinib treatment groups to 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.

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

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

Pharmacokinetic:

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

Statistical Methods (Continued):
Safety:

Safety analyses will be carried out using the Safety Analysis Set, which includes all subjects who receive at least one dose of study drug. There will be two sets of planned safety analyses: safety analysis by Week 24, and long-term safety analysis. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from baseline to defined time points will be tabulated.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ACR	American College of Rheumatology
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALC	Absolute Lymphocyte Count
ALT	ALT
ANC	Absolute Neutrophil Count
Anti-CCP	Anti-Cyclic Citrullinated Peptide
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate Transaminase
AUC	Area under the plasma concentration-time curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BCG	Bacillus Calmette-Guerin
bDMARD	Biological Disease Modifying Anti-Rheumatic Drug
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CBC	Complete Blood Count
CCP	Cyclic Citrullinated Peptide
CDAI	Clinical Disease Activity Index
CL/F	Apparent Clearance
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
COVID-19	Coronavirus Disease – 2019
CRF	Case Report Form
CS	Clinically Significant
csDMARD	Conventionally synthetic Disease Modifying Anti-Rheumatic Drug
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-Ray
CYP3A	Cytochrome P450 3A

DAPSA	Disease Activity In Psoriatic Arthritis
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
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EOW	Every Other Week
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQoL-5 Dimensions – 5 Levels
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCQ	Hydroxychloroquine
HCV Ab	Hepatitis C Virus Antibody
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HRU	Health Resource Utilization
hs-CRP	High-Sensitivity C Reactive Protein
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IR	Inadequate Response

IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
JAK	Janus Kinase
LDA	Low Disease Activity
LDI	Leeds Dactylitis Index
LDL-C	Low-Density Lipoprotein Cholesterol
LEF	Leflunomide
LEI	Leeds Enthesitis Indicies
MACE	Major Adverse Cardiovascular Event
MD	Medical Director
MDA	Minimal Disease Activity
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
N	Number
NCS	Not Clinically Significant
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
OL	Open-label
PASI	Psoriasis Area Severity Index
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PCS	Physical Component Summary
PD	Premature Discontinuation
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PPD	Purified Protein Derivative
PRN	As Needed (Latin: Pro Re Nata)

PRO	Patient-Reported Outcome
PsA	Psoriatic Arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsO	Psoriasis
PT	Preferred Term
PtGA	Patient's Global Assessment of Disease Activity
PUVA	Psoralens and Ultraviolet A
QD	Once Daily (Latin: Quaque Die)
QoL	Quality of Life
QTc	QT interval corrected for heart rate
RA	Rheumatoid Arthritis
RAVE	EDC System from Medidata
RBC	Red Blood Count
RCT	Randomized Controlled Trial
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAPS	Self-Assessment of Psoriasis Symptoms
SF-36	36-Item Short Form Health Survey
SHS	Sharp/van der Heijde Score
sIGA	Static Investigator Global Assessment of Psoriasis
SJC	Swollen Joint Count
SOC	System Organ Class
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2T	Treat-To-Target
TA	Therapeutic Area
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TBD	To Be Determined
TEAE	Treatment emergent adverse event
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor

Tyk2	Tyrosine kinase 2
ULN	Upper Limit of Normal
UVA	Ultraviolet A
UVB	Ultraviolet B
V/F	Apparent Volume of Distribution
WBC	White Blood Cell
WPAI	Work Productivity and Activity Impairment

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3.0 Introduction

Psoriatic Arthritis

Psoriatic Arthritis (PsA) is a chronic systemic inflammatory disease classified as a sub-type of spondyloarthritis (SpA) and characterized by the association of arthritis and psoriasis. PsA can develop at any time, but for most people it appears between the ages of 30 and 50, and it affects men and women equally.[1] The course of PsA is usually characterized by flares and remissions.[1] Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, disability, and a reduced life expectancy.[1,2] For most patients, skin manifestations predate the arthritis.[1]

Patients with PsA experience varying combinations of disease manifestations affecting the synovium, tendons, entheses, skin, and bone. These manifestations of disease range in prevalence with peripheral arthritis and variable degrees of psoriasis observed in all patients at some point during their disease course, axial disease in 40 – 74% depending on the criteria used for diagnosis,[3] enthesitis in 25 – 51%, dactylitis in 8 – 59%[4-6] and anterior uveitis in 2 – 25%.[7] Additionally, PsA patients are more likely to experience the co-morbid conditions of cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, inflammatory bowel disease, kidney disease, osteoporosis, fibromyalgia,[8] depression, and anxiety than healthy subjects,[9] and have decreased quality of life and functional impairment.[10,11]

The prevalence of PsA varies by region and has been reported as 0.13% in North America, 0.07% in South America, 0.19% in Europe, 0.01 – 0.07% in Africa, the Middle East, and Asia.[12]

PsA patients require treatment of the entire spectrum of disease manifestations. The primary goal of treating patients with PsA is to maximize long-term health-related quality of life, through control of symptoms, prevention of structural damage, normalization of function and social participation and abrogation of inflammation. Initial treatment of musculoskeletal symptoms is composed of nonsteroidal anti-inflammatory drugs

(NSAIDs) and local corticosteroid injections, while topical therapies are used for the initial treatment of psoriasis. For patients who experience lack of efficacy or toxicity with these measures, for the treatment of peripheral arthritis, both the European League Against Rheumatism (EULAR)[13] and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)[14] recommend systemic therapy with conventional disease modifying anti-rheumatic drugs (cDMARDs) (methotrexate [MTX], leflunomide [LEF], sulfasalazine [SSZ], or ciclosporin A), followed by anti-tumor necrosis factor (TNF) therapy in patients who do not respond adequately to cDMARDs. Other biologic therapies (e.g., IL-12/23 or IL-17 inhibitors) are also recommended as alternatives to anti-TNF inhibitors in selected PsA patients. Additional specific recommendations differ slightly between EULAR and GRAPPA, however recommendations for therapeutic choice are made based on a patient's clinical presentation as some manifestations of PsA, such as enthesitis, dactylitis, and axial disease are either not responsive or poorly responsive to cDMARDs. Additional therapeutic options are also recommended specifically for treatment of skin disease.[13,14]

Despite the beneficial results achieved with currently available biologic agents, approximately 40% of patients do not have at least 20% improvement in American College of Rheumatology (ACR) scores[13,15-21] and only 58%[22] to 61%[23] of patients with PsA who receive them are able to achieve clinical remission after 1 year of treatment, with only approximately 43% achieving sustained remission for at least 1 year.[24] Thus, there remains a clear medical need for additional therapeutic options in PsA for patients with inadequate response to or intolerance to currently available therapies.

Targeting the Janus kinase (JAK) signaling pathway for autoimmune diseases, such as PsA, rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis (UC), and atopic dermatitis, is supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. The activation of JAK signaling 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.[25,26]

The JAK family is composed of 4 members: JAK1, 2, 3, and tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases act in tandem to activate the Signal Transducer and Activator of Transcription (STAT) that transduce cytokine-mediated signals, and are associated with multiple membrane cytokine receptors such as common gamma-chain (CGC) receptors and the glycoprotein 130 trans-membrane proteins.[27] JAK3 and JAK1 are components of the CGC cytokine receptor complexes that are responsible for the signaling of the inflammatory cytokines IL-2, -4, -7, -9, -15 and -21; whereas IL-12 and IL-23 signal through JAK2 and Tyk2.[28] Propagation of these signals is important in the amplification of inflammatory responses. While the exact mechanism of PsA has not been fully elucidated, multiple cytokines such as IL-1, -6, -12, -17, -20, and -23 are thought to be involved in the activation and proliferation of epidermal keratinocytes in psoriatic lesions.[29] The IL 17/IL-23 cytokine axis is also thought to be important in PsA pathogenesis.[30] Thus, blockade of either JAK1 or Tyk2 could inhibit the response of central cytokine signals thought to be important in the pathogenesis of PsA.

Tofacitinib is an oral JAK inhibitor that inhibits JAK1, JAK2, and JAK3 with high in vitro functional specificity for kinases 1 and 3. Tofacitinib is currently in Phase 3 development in PsA. The Phase 3 studies evaluated the efficacy and safety of tofacitinib 5 mg and 10 mg twice daily (BID) in adult patients with active PsA who had an inadequate response to at least one conventional synthetic DMARD (csDMARD) and who were TNF inhibitor-naïve (OPAL Broaden) or who had an inadequate response to at least 1 TNF inhibitor (OPAL Beyond). Both studies achieved the primary endpoints of ACR20 and change in Health Assessment Questionnaire Disability Index (HAQ DI) versus placebo for both the 5 mg BID and 10 mg BID doses at Month 3. Data reported from OPAL Broaden indicate ACR20 response at Month 3 for placebo, tofacitinib 5 mg BID, tofacitinib 10 mg BID, and adalimumab 40 mg EOW of 33.3%, 50.5%, 60.6%, and 51.9%, respectively; p-value versus placebo for each active therapy was ≤ 0.05. At Month 3, statistically significant results in favor of tofacitinib over placebo for both dose groups were also observed for ACR50/70 responses, and PASI75 response. Superiority of tofactinib versus placebo was seen in the Leeds Enthesitis Index (LEI), and Dactylitis Severity Score (DSS) at the 10 mg BID dose only. Results for the primary and reported

secondary efficacy endpoints were maintained to Month 12. No radiographic data were reported at Month 3 (end of double-blind period); however at Month 12 little radiographic progression was observed in any dose group.[31] OPAL Beyond results for ACR20 response at Month 3 for placebo, tofacitinib 5 mg BID, and tofacitinib 10 mg BID were 23.7%, 49.6%, and 47.0%, respectively; p-value versus placebo for each active therapy was ≤ 0.0001. At Month 3 statistically superior results in favor of tofacitinib at both doses versus placebo for ACR50, LEI, and DSS were also observed with superiority over placebo for PASI75 demonstrated only at the 10 mg BID dose while ACR70 response was not significantly different from placebo for either dose group.[32] The observed safety findings for both studies were consistent with those observed in the RA and psoriasis development programs. In related diseases (RA,[1] psoriasis,[33] and ankylosing spondylitis[34]), tofacitinib has demonstrated an impact on signs and symptoms, as measured by ACR, Psoriasis Area and Severity Index (PASI), and Assessment in Ankylosing Spondylitis (ASAS) response criteria.[31-35]

Upadacitinib is a novel JAK1 inhibitor being developed for the treatment of adult patients with inflammatory diseases. Based on in vitro selectivity assays and in vivo animal models, upadacitinib has demonstrated inhibition of JAK1 at efficacious drug exposure levels that spare an inhibitory effect on JAK2. The enhanced selectivity of upadacitinib may have the potential for an improved benefit/risk profile by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis.

Upadacitinib Clinical Development

To date, single and multiple doses of upadacitinib have been studied in healthy volunteers in 10 Phase 1 studies (one of which also employed a substudy in subjects with mild to moderate RA), which have completed study conduct. In addition, upadacitinib has been studied in 4 Phase 2 trials in subjects with RA or Crohn's disease. Two of these Phase 2 trials have completed study conduct: 2 randomized controlled trials (RCTs) in 575 subjects with moderately to severely active RA on background MTX (Studies M13-550 and M13-537). One open-label extension to the completed RA studies (Study M13-538) and 1 randomized, dose-ranging, placebo-controlled study

(Study M13-740) in subjects with moderately to severely active Crohn's disease with a history of inadequate response to or intolerance to anti-TNF therapy are ongoing. The RA Phase 3 clinical development program has been initiated and will include 6 randomized, controlled studies followed by long-term extension periods.

No Phase 2 studies in subjects with PsA have been performed with upadacitinib. Results from the Phase 2 randomized controlled studies in subjects with RA are available. Efficacy of treatment with upadacitinib in patients with moderate to severe RA was demonstrated in both Phase 2 Studies M13-550 and M13-537. Results from both studies demonstrated dose- and exposure-dependent improvement in clinical signs and symptoms as measured by the ACR20/50/70 response criteria.

The Phase 2 program for upadacitinib in subjects with moderately to severely active RA consisted of 2 randomized controlled trials (RCTs), both on stable background methotrexate (MTX) therapy, 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 low disease activity (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 clinical remission at Week 12.

Safety results across the studies showed that upadacitinib was well tolerated and the types and frequencies of adverse events (AEs) were consistent with subjects with moderately to severely active RA receiving immunomodulatory therapy. One subject died from lung cancer 14 weeks after completing the 12-week study (Study M13-537); the lung cancer was considered by the investigator as not related to study drug. This subject had a 40 pack-year history of tobacco use and a positive family history of lung cancer. The rates of serious adverse events (SAEs) and AEs resulting in discontinuation of study drug were low and not significantly different from placebo. No trends in the number of subjects with potentially clinically significant values or changes per dose group were observed for any of the hematology or urine parameters; however, treatment-emergent increases in blood creatine phosphokinase (CPK), all of which were asymptomatic, were reported with higher doses of upadacitinib (12 to 18 mg BID). No subject discontinued study drug due to elevated CPK. In all subjects, the CPK values normalized or were significantly reduced at the time of last observation. Among subjects with laboratory evidence of systemic inflammation (as evidenced by C-reactive protein [CRP] > upper limit of normal [ULN]), treatment with upadacitinib 3 mg BID or 6 mg BID was associated with improvements in mean hemoglobin (Hgb) relative to placebo. At higher doses, there was a reduction in mean Hgb, however the reduction was not clinically significant, as mean Hgb levels remained within normal range throughout the treatment period. One subject each in the 18 mg BID group in both Study M13-550 and Study M13-537 had an AE of anemia. Overall, the AEs observed during the Phase 2 development, as well as changes in physical examination findings, vital signs and clinical laboratory results, do not indicate any safety concerns for further development of upadacitinib.

Phase 3 Studies with Upadacitinib

Six multi-country randomized controlled trials (RCTs) inclusive of approximately 4,425 subjects are planned or ongoing for upadacitinib in subjects with moderately to severely active RA. Study M13-542 (NCT02706847) will enroll subjects who had an inadequate response to biologic DMARDs. Study M15-925 (NCT TBD) will compare upadacitinib vs. abatacept in subjects who had an inadequate response to biologic DMARDs. Study M13-549 (NCT02675426) will enroll subjects who are on a stable dose of conventional synthetic DMARD (csDMARD) and have an inadequate response to csDMARDs. Study M14-465 (NCT02629159) will enroll subjects who are on a stable dose of MTX and have an inadequate response to MTX. Study M13-545 (NCT02706873) will enroll subjects who are MTX naïve. Study M15-555 (NCT02706951) will enroll subjects who had an inadequate response to MTX and will investigate the use of upadacitinib as monotherapy. A total of 3 dose regimens of upadacitinib once-daily tablets [30 mg QD, 15 mg QD, and 7.5 mg QD (Japan only)] will be evaluated. There are no data available from these studies at this time.

3.1 Differences Statement

This study is the first to evaluate the safety, tolerability, and efficacy of upadacitinib in subjects with PsA who have had an inadequate response to at least one bDMARD.

3.2 Benefits and Risks

Despite the availability of various PsA therapies, including conventional synthetic (cs)DMARDs, 1 targeted synthetic (ts)DMARD and biologic (b)DMARDs, many patients still do not respond adequately to these treatments, or gradually lose response over time. There is evidence for clinical benefit of JAK inhibition in PsA based on 2 Phase 3 studies of tofacitinib, a non-selective JAK inhibitor.[31,32] Many AEs (serious infections, herpes zoster reactivation, malignancies, and hematologic adverse events) observed for tofacitinib are thought to be a consequence of non-selectivity against the members of the JAK family of proteins. 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. A 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.[36-46] Together, the safety and efficacy data from the Phase 2 RA program and establishment of proof of concept for efficacy of JAK inhibition in PsA (with tofacitinib) support further development of upadacitinib in Phase 3 in subjects with PsA.

The safety profile specific to upadacitinib is evolving with safety results to date consistent with those known to be associated with JAK inhibition. Adverse events in the categories of infection such as urinary tract infection, upper respiratory tract infection and herpes zoster reactivation have been reported as well as adverse events in the categories of malignancies, and gastrointestinal disorders such as gastrointestinal perforation. Events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including upadacitinib.

In addition, laboratory changes including elevations of liver function tests, increase in lipids, elevation in serum creatinine, creatine phosphokinase, reduced hemoglobin depending on baseline inflammatory burden, lower white blood cell counts, and reductions in Natural Killer (NK) cells have been observed with upadacitinib therapy.

The results of all genetic toxicology testing indicate that upadacitinib is not genotoxic, however upadacitinib is teratogenic based on animal studies, which necessitates avoidance of pregnancy in women of childbearing potential. Based on the calculated safety margins for human fetal exposure with seminal fluid transfer, there is judged to be no risk to the pregnancy of female partners of male subjects who are treated with upadacitinib.

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology and safety experience with upadacitinib can be found in the current Investigator's Brochure.

4.0 Study Objective

Period 1

1. To compare the efficacy of upadacitinib 15 mg once daily (QD) and 30 mg QD versus placebo for the treatment of signs and symptoms in subjects with moderately to severely active PsA who have an inadequate response or intolerance to bDMARDs (Bio-IR).
2. To compare the safety and tolerability of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have an inadequate response or intolerance to bDMARDs.

Period 2

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

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3 multicenter study that includes two periods. Period 1 is 56-weeks in duration and includes a 24-week randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo in subjects with moderately to severely active PsA who have an inadequate response to bDMARDs (Bio-IR). Period 2 is an open label (blinded until the last subject completes the last visit of Period 1) long-term extension of up to a total treatment duration of approximately 3 years to evaluate the safety, tolerability and efficacy of upadacitinib 15 mg QD, and 30 mg QD, in subjects with PsA who have completed Period 1.

Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

The study is designed to enroll approximately 630 subjects at approximately 165 study centers worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

The study duration will include a 35-day screening period; a 56-week blinded period which includes 24 weeks of double-blind, placebo-controlled treatment followed by 32 weeks of treatment blinded to dose of upadacitinib (Period 1); a long-term extension period of up to a total treatment duration of approximately 3 years ([blinded until the last subject completes the last visit of Period 1] Period 2); and a 30-day follow-up call or visit.

Subjects who meet eligibility criteria will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, and number of prior failed (had an inadequate response to) biologic DMARDs (1 vs > 1), except for subjects from Japan, for which randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA) only, and then randomized in a 2:2:1:1 ratio to one of four treatment groups:

Group 1: upadacitinib 15 mg QD (N = 210)

Group 2: upadacitinib 30 mg QD (N = 210)

Group 3: Placebo followed by upadacitinib 15 mg QD (N = 105)

Group 4: Placebo followed by upadacitinib30 mg QD (N = 105)

No more than approximately 40% of subjects will be enrolled with < 3% BSA extent of psoriasis and no more than approximately 30% of subjects will be enrolled with prior failure of more than 1 biologic DMARD.

Subjects will receive oral study drug QD (upadacitinib 15 mg, upadacitinib 30 mg, or matching placebo) until the end of the study or they discontinue study drug.

Subjects who were assigned to placebo at Baseline will be preassigned to receive either upadacitinib 15 mg QD or upadacitinib 30 mg QD starting at Week 24 in a 1:1 ratio. Subjects who complete the Week 56 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (total treatment up to approximately 3 years). Subjects will continue study treatment as assigned in Period 1. Subjects will continue to receive upadacitinib 15 mg QD or upadacitinib 30 mg QD, respectively, in a blinded manner until the last subject completes the last visit of Period 1 (Week 56), when study drug assignment in both periods will be unblinded to the sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2. Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

Subjects must have had inadequate response to ≥ 1 bDMARD prior to the Screening visit and must have discontinued all bDMARDs prior to the first dose of study drug. No background non-biologic DMARD therapy is required during participation in this study. For subjects who are on non-biologic DMARD therapy at baseline (methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), apremilast, hydroxychloroquine (HCQ), bucillamine or iguratimod), non-biologic DMARDs should have been started ≥ 12 weeks prior to baseline visit, must be at stable dose for ≥ 4 weeks prior to the first dose of study drug and remain at stable dose through Week 36 of the study; the non-biologic DMARD dose may be decreased only for safety reasons. In addition, all subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Please refer to Section 5.2.3.2 for additional details related to prior and concomitant DMARD therapy.

At Week 16, rescue therapy will be offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) as follows: 1) add or

modify doses of non-biologic DMARDs, NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), oral corticosteroids and/or 2) receive 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint, 1 trigger point, 1 tender point, 1 bursa, or 1 enthesis as described in Section 5.2.3.4 (Rescue Therapy).

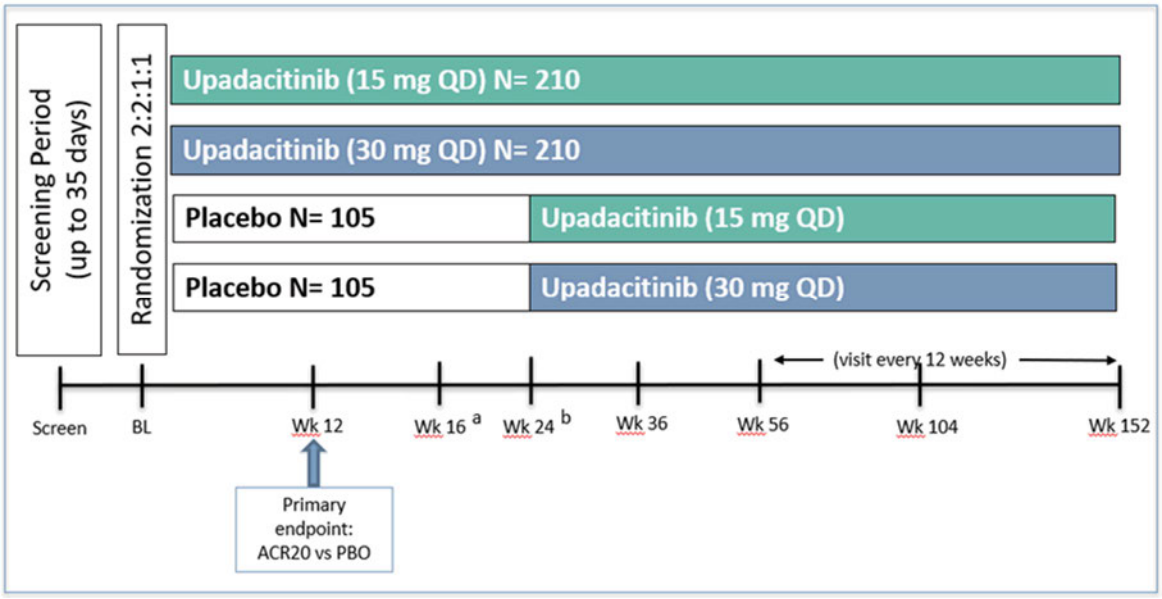
At Week 24, all subjects allocated to placebo at Baseline will be switched to blinded upadacitinib (randomized at baseline to either 15 mg QD or 30 mg QD) treatment regardless of clinical response.

After the last subject completes the Week 24 study visit, an unblinded analysis will be conducted for the purpose of initial regulatory submission. To maintain integrity of the trial during the blinded 56-week period study sites and subjects will remain blinded until all subjects have reached Week 56. A second unblinded analysis may be conducted for regulatory purposes after all subjects have completed Period 1. A final analysis will be conducted after all subjects have completed Period 2.

Starting at Week 36, subjects who fail to demonstrate at least 20% improvement in either or both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment. Additionally, in subjects continuing on study drug, starting at the Week 36 visit (after Week 36 assessments have been performed), initiation of or change in background PsA medication(s) including oral corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, low potency opiates, and non-biologic DMARDs (concomitant use of up to 2 non-biologic DMARDs except the combination of MTX and leflunomide), is allowed as per local label with maximum doses as outlined in Section 5.2.3.3.

A schematic of the overall study design is shown in Figure 1 below.

Figure 1. Study Design



a. At Week 16 rescue therapy will be offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) as described in Section 5.2.3.4.

b. At Week 24, all placebo subjects will switch to upadacitinib 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

Note: Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

Screening Period

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

Subjects that initially screen-fail for the study are permitted to re-screen once following re-consent without prior AbbVie approval. 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 HBV, HCV and HIV serology, the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold test) and/or a purified protein derivative (PPD) test (or equivalent) (or both if required per local guidelines), chest x-ray, and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.3.1.1 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. X-rays of hands and feet may be repeated although will not be required during re-screening.

Period 1 (56-Week Randomized, Double-Blind Treatment Period)

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 56 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 Baseline (Day 1), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 44 and 56. A ± 3 day window is permitted around scheduled study visits up to Week 36. Following Week 36, a ± 7 day window is permitted. The last dose of oral study drug in Period 1 is taken the day prior to the Week 56 visit.

Period 2 (Long-Term Extension Period [up to a Total Treatment Duration of Approximately 3 Years])

Period 2 will begin at the Week 56 visit after all assessments have been completed. When the last subject completes the last visit of Period 1 (Week 56), study drug assignment in both periods will be unblinded to the sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2. During Period 2, subjects will have a

study visit at Week 56 and every 12 weeks thereafter until completion of the study. A ± 7 day window is permitted around scheduled study visits.

The last dose of oral study drug is taken the day prior to the Week 152 visit.

Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

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

Starting at Week 36, subjects who failed to show at least 20% improvement in either or both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment. Subjects who discontinue study drug treatment may choose to continue to participate in the study (refer to Section 5.4.1 for additional details). Subjects who prematurely discontinue study drug should complete a Premature Discontinuation visit (PD visit) as soon as possible, preferably within 2 weeks of study drug discontinuation and preferably prior to initiation of another therapy. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix C and adhere to all study procedures except for dispensing study drug, annual TB testing, PK sample collection, blood sample collection for optional exploratory research and validation studies, and calculation for drug assignment based on TJC/SJC. If a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

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

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time (refer to Section 5.4.2 for additional details). If a subject prematurely discontinues study drug treatment and study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug

discontinuation and preferably prior to initiation of another therapy. In addition, a 30-day follow-up visit (or phone call if a visit is not possible) should occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Follow-Up Period

Subjects who complete the last visit of Period 2 (Week 152) will have a follow-up visit approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AEs and to collect vital signs and clinical laboratory tests. The 30 day follow-up visit is not required for subjects who discontinued study drug and continued study participation with completion of at least one study visit approximately 30 days after last dose of study drug.

5.2 Selection of Study Population

It is anticipated that approximately 630 subjects with active PsA despite prior use of at least one bDMARD will be randomized at approximately 165 study centers, globally.

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria specified in Section 5.2.1 and none of the exclusion criteria specified in Section 5.2.2 of this protocol.

5.2.1 Inclusion Criteria

1. Adult male or female, at least ≥ 18 years old at Screening.
2. Clinical diagnosis of PsA with symptom onset at least 6 months prior to the Screening Visit and fulfillment of the Classification Criteria for PsA (CASPAR).
3. Subject has active disease at Baseline defined as ≥ 3 tender joints (based on 68 joint counts) and ≥ 3 swollen joints (based on 66 joint counts) at Screening and Baseline Visits.
4. Diagnosis of active plaque psoriasis or documented history of plaque psoriasis.

5. Subject has had an inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to treatment with at least 1 bDMARD.

6. Subjects must have discontinued all bDMARDs prior to the first dose of study drug. Subjects who need to discontinue bDMARDs prior to the Baseline Visit to comply with this inclusion criterion must follow the procedure specified below or at least five times the mean terminal elimination half-life of a drug:

   - ≥ 4 weeks for etanercept;
   - ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and ixekizumab;
   - ≥ 16 weeks for secukinumab;
   - ≥ 12 weeks for ustekinumab;
   - ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pretreatment level or normal reference range (local lab) if pretreatment levels are not available.

7. Subject who is on current treatment with concomitant non-biologic DMARDs at study entry must be on ≤ 2 non-biologic DMARDs (except the combination of MTX and leflunomide) at the following doses: MTX (≤ 25 mg/week), SSZ (≤ 3000 mg/day), leflunomide (LEF) (≤ 20 mg/day), apremilast (≤ 60 mg/day), HCQ (≤ 400 mg/day), bucillamine (≤ 300 mg/day) and iguratimod (≤ 50 mg/day) for ≥ 12 weeks and at stable dose for ≥ 4 weeks prior to the Baseline Visit. No other DMARDs are permitted during the study.

   - Subjects who need to discontinue DMARDs prior to the Baseline Visit to comply with this inclusion criterion must follow the procedure specified below or at least five times the mean terminal elimination half-life of a drug:
     - ≥ 8 weeks for LEF if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine, or 30 days washout with activated charcoal or as per local label);
     - ≥ 4 weeks for all others.

8. Stable doses of NSAIDs, acetaminophen/paracetamol, low-potency opiates (tramadol or combination of acetaminophen and codeine or hydrocodone), oral

corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids for stable medical conditions are allowed, but must have been at a stable dose for ≥ 1 weeks prior to the Baseline Visit.

9. Subjects must have discontinued all opiates (except for tramadol or combination of acetaminophen and codeine or hydrocodone) at least 1 week and oral Traditional Chinese Medicine for at least 4 weeks prior to the first dose of study drug (refer to Section 5.2.3.3 for prohibited medications).

10. Women of childbearing potential (refer to Section 5.2.4), must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing.

    Note: Subjects with a borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.

11. If female, subject must be postmenopausal OR permanently surgically sterile OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control (Section 5.2.4), that is effective from the Baseline visit through at least 30 days after the last dose of study drug.

    - Additional local requirements may apply. Refer to Appendix G for local requirements.

12. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. For subjects in Japan only: if a subject is under 20 years of age, then the subject and their parent or legal guardian must voluntarily sign and date an informed consent.

Rationale for Inclusion Criteria

1 – 9	To select the appropriate subject population
10, 11	The effect of upadacitinib on pregnancy and reproduction is unknown
12	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Prior exposure to any Janus Kinase (JAK) inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, and filgotinib).
2. Current treatment with > 2 non-biologic DMARDs or use of DMARDs other than MTX, SSZ, LEF, apremilast, HCQ, bucillamine or iguratimod or use of MTX in combination with LEF at Baseline.
3. 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 interventional clinical study.
4. Current or past history of infection including:
   - History of recurrent or disseminated (even a single episode) herpes zoster;
   - History of disseminated (even a single episode) herpes simplex;
   - History of known invasive infection (e.g., listeriosis and histoplasmosis);
   - Active human immunodeficiency virus (HIV) or immunodeficiency syndrome. Active HIV is defined as confirmed positive anti-HIV antibody (HIV Ab) test;
   - Subject has active TB or meets TB exclusionary parameters (refer to Section 5.3.1.1 for specific requirements for TB testing);
   - *For subjects in Japan only: Positive result of beta-D-glucan or two consecutive indeterminate results of beta-D-glucan (screening for pneumocystis jiroveci infection);*
   - Active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit;
   - Chronic recurring infection and/or active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study;
   - Active HBV or HCV defined as:

- HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects (and for Hepatitis B surface antibody positive [+] subjects in Japan or where mandated by local requirements);
- HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).

5. Underlying medical diseases or problems including but not limited to the following:

- History of any of the following cardiovascular conditions:
  - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
  - Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
- Subject has been a previous recipient of an organ transplant which requires continued immunosuppression;
- History of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment;
- Conditions that could interfere with drug absorption including but not limited to short bowel syndrome;
- History of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix;
- History of clinically significant medical conditions or any other reason which 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 or would put the subject at risk by participating in the protocol; or permanently wheelchair-bound or bedridden or very poor functional status which prevents the ability to perform self-care.

6. Use of the following concomitant psoriasis treatments within the specified timeframe prior to Baseline Visit:

- Oral retinoids within 4 weeks of the Baseline visit;
- Fumarates within 1 week of the Baseline visit;
- Psoralens and Ultraviolet A (PUVA) within 4 weeks of the Baseline visit;
- Ultraviolet A (UVA) or Ultraviolet B (UVB), or Laser therapy within 2 weeks of the Baseline visit;
- All topical psoriasis treatments, including medicated shampoos, within 2 weeks of the Baseline visit. The following exceptions are allowed:
  - Bland (without beta or alpha hydroxy acids, urea or salicyclic acids) emollients
  - Low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only.
  - Topical anti-itch treatments with no expected effect on psoriatic skin lesions.

7. Systemic use of known strong cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers from Screening through the last dose of the study drug (refer to Table 1 for examples of commonly used strong CYP3A inhibitors and inducers).
8. Receipt of any live vaccine within 4 weeks (8 weeks in Japan) prior to the Baseline Visit, or expected need of live vaccination during study participation including at least 4 weeks (8 weeks in Japan) after the last dose of study drug.
9. Subject has received oral or parenteral Traditional Chinese Medicines within 4 weeks prior to Baseline, has received opioid analgesics (except for tramadol or combination of acetaminophen and codeine or hydrocodone which are allowed) within 1 week prior to Baseline, or used of inhaled marijuana within 2 weeks prior to Baseline.
10. History of an allergic reaction or significant sensitivity to constituents of the study drugs (or its excipients) and/or other products in the same class.
11. History of any fibromyalgia, any arthritis with onset prior to age 17 years, or diagnosis of inflammatory joint disease other than PsA (including, but not limited to rheumatoid arthritis, gout, overlap connective tissue diseases, scleroderma,

polymyositis, dermatomyositis, systemic lupus erythematosus). Prior history of reactive arthritis or axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis is permitted if documentation of change in diagnosis to PsA or additional diagnosis of PsA is made. Prior history of fibromyalgia is permitted if documentation of change in diagnosis to PsA or documentation that the diagnosis of fibromyalgia was made incorrectly.

12. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.

13. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or within 30 days after the last dose of study drug.

14. Laboratory values meeting the following criteria within the Screening period:

- Serum aspartate transaminase (AST) > 2 × ULN;
- Serum alanine transaminase (ALT) > 2 × ULN;
- Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m^2;
- Total white blood cell count (WBC) < 2,500/μL;
- Absolute neutrophil count (ANC) < 1,500/μL;
- Platelet count < 100,000/μL;
- Absolute lymphocyte count < 800/μL;
- Hemoglobin < 10 g/dL.

15. Active skin disease other than psoriasis that would interfere with the assessment of psoriasis.

16. Subject with extra-articular manifestations of PsA (e.g., PsO, uveitis, or IBD) that are not clinically stable for at least 30 days prior to study entry.

17. Subject has had joint surgery at joints to be assessed within this study or 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 Baseline visit.

18. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive upadacitinib.

The Rationale for the Exclusion Criteria

1 – 3, 11	To select the appropriate subject population
13	The impact of upadacitinib on pregnancies is unknown
4 – 10, 12, 14 – 18	To ensure safety of the subjects throughout the study

5.2.3 Prior, Concomitant, and Prohibited Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements including folic acid) that the subject is receiving within 28 days prior to Screening and/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 must be recorded in the eCRF.

Vaccines

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap). It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks (8 weeks in Japan) before first dose of study drug or administered at least 30 days after last dose of oral study drug. If the herpes zoster vaccine is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing immunity to varicella should be confirmed with antibody testing at or prior to screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative the herpes zoster vaccine should not be administered. See Section 5.2.3.3 for a list of commonly used live vaccines.

The AbbVie Therapeutic Area Medical Director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior Therapy

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

5.2.3.2 Permitted Background Therapy

In Period 1, if subjects are on background DMARDs they should continue on their stable background treatment of up to 2 non-biologic DMARDs (DMARDs should have been started ≥ 12 weeks prior to the Baseline visit and without dosing or administration changes ≥ 4 weeks prior to the Baseline visit). The following non-biologic DMARDs are permitted as background therapy during the study: MTX (≤ 25 mg/week), SSZ (≤ 3000 mg/day), leflunomide (LEF) (≤ 20 mg/day), apremilast (≤ 60 mg/day), HCQ (≤ 400 mg/day), bucillamine (≤ 300 mg/day) and iguratimod (≤ 50 mg/day). In addition, for all subjects taking MTX, subjects should take a dietary supplement of oral folic acid (or equivalent, such as folinic acid) throughout study participation. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions. No other DMARDs are permitted during the first 36 weeks of study participation in Period 1. At any time, the background DMARD dose may be decreased for safety reasons. AbbVie will not provide background DMARDs or folic acid.

In the first 36 weeks of study participation in Period 1, subjects should also continue on their stable doses of NSAIDs, acetaminophen/paracetamol, low-potency opiates (tramadol or combination of acetaminophen with codeine or hydrocodone), oral corticosteroids (equivalent to prednisone ≤ 10 mg/day). If taking any of the above on a scheduled basis, they should continue to take them as they did at study entry with no change in dose or frequency, including on study visit days. If not taking any of the above at baseline, these

should not be initiated except where permitted by protocol (specific time period or protocol-defined rescue). If taking any of the above at baseline on an as-needed basis (PRN), they should continue to use them for the same reason and same dose each time but they should not be taken within the 24 hours prior to any study visit to avoid bias in outcome measurements. In the event of tolerability (or other safety) issues, these medications may be decreased, or discontinued with substitution of another permitted medication from that class. PRN use of inhaled corticosteroids is permitted at any time.

In Periods 1 and 2, starting at Week 36 (after Week 36 assessments have been performed) and thereafter, 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath injections of corticosteroids, dosage and frequency per standard of care, is allowed every 12 weeks. However, corticosteroid injections should be avoided within 21 days prior to the next scheduled study visit to avoid confounding effects of systemic absorption of intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids.

In addition, at Week 36 (after Week 36 assessments have been performed) and thereafter, initiation of or change in oral corticosteroids, NSAIDs, acetaminophen/paracetamol, low-potency opiates (tramadol or combination of acetaminophen with codeine or hydrocodone) or adding or changing doses of non-biologic DMARDs (MTX, LEF, SSZ, apremilast, HCQ, bucillamine or iguratimod) is allowed as per local label. Concomitant use of up to 2 non-biologic DMARDs (MTX, LEF, SSZ, apremilast, HCQ, bucillamine or iguratimod) except the combination of MTX and LEF is permitted. Doses of non-biologic DMARDs and oral corticosteroids may not exceed maximums defined above and in inclusion criteria (Section 5.2.1).

After the Week 16 visit has been completed, a subject who qualifies for rescue therapy will be permitted to add or modify doses of non-biologic DMARDs, NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), oral corticosteroids and/or receive 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint, 1 trigger point, 1 tender point, 1 bursa, or 1 enthesis as

described in Section 5.2.3.4 (Rescue Therapy). Corticosteroid injections should be avoided within 21 days prior to the next scheduled study visit to avoid confounding effects of systemic absorption of corticosteroids.

In Period 1 and Period 2 permitted topical treatments for Psoriasis (PsO) include:

- Non-medicated shampoos
- Bland (without beta or alpha hydroxy acids, urea or salicylic acid) emollients
- Low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only.

Starting at Week 16 (after Week 16 assessments have been performed) and thereafter, subjects may use any therapy for PsO per investigator judgment, with the exception of non-biologic DMARDs which may not be initiated or modified at Week 16 unless non-responder criteria are met as detailed in Section 5.2.3.4 Rescue Therapy. At Week 36 and thereafter, initiation of or change in dose of non-biologic DMARDs is permitted as described above.

5.2.3.3 Prohibited Therapy

Non-Biologic DMARDs

Prior exposure to or concomitant use of JAK inhibitors (including but not limited to ruxolitinib [Jakafi®], tofacitinib [Xeljanz®], baricitinib, and filgotinib) is not allowed.

Use of MTX in combination with LEF is NOT allowed.

Concomitant therapy with > 2 non-biologic DMARDs or therapy with DMARDs other than MTX (≤ 25 mg/week), SSZ (≤ 3000 mg/day), leflunomide (LEF) (≤ 20 mg/day), apremilast (≤ 60 mg/day), HCQ (≤ 400 mg/day), bucillamine (≤ 300 mg/day) or iguratimod (≤ 50 mg/day). Subjects must have discontinued all other non-biologic DMARDs prior to Baseline Visit as specified in Inclusion Criterion 7, Section 5.2.1.

Corticosteroids

Intravenous (IV), intramuscular (IM), and epidural corticosteroids are NOT allowed.

Biologic Therapies

All prior and concomitant biologic therapies, and biosimilar versions of biologic drugs for treatment of PsA are prohibited during the study (Period 1 and Period 2). 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)
- Taltz® (ixekizumab)
- Cosentyx® (secukinumab)

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. The most commonly used strong CYP3A inhibitors and inducers are listed in Table 1.

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

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

Cannabis

Use of inhaled medicinal and recreational marijuana is prohibited during the study and subjects must have discontinued use at least 2 weeks prior to Baseline.

Opiates

Opiates, with the exception of tramadol or combination of acetaminophen and codeine or hydrocodone, are not permitted during the study, and subjects must have discontinued prohibited opiates at least 1 week prior to the first dose of study drug, including (but not limited to):

- buprenorphine
- codeine
- fentanyl
- hydrocodone
- hydromorphone
- levorphanol
- meperidine
- methadone
- morphine
- oxycodone
- oxymorphone
- propoxyphene

Low potency opioid medications limited to tramadol or combination of acetaminophen and codeine or hydrocodone are permitted during the study.

Traditional Chinese Medications

Oral or parenteral Traditional Chinese Medicine is not permitted during the study, and subjects must have discontinued Traditional Chinese Medicines at least 4 weeks prior to the first dose of study drug. Subjects may not use oral or parenteral Traditional Chinese Medicines during the study including for treatment of AEs.

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 at least 4 weeks (8 weeks in Japan) before first dose of study drug. 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 attenuated influenza A (H1N1) (intranasal)
- Seasonal trivalent live attenuated 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.

5.2.3.4 Rescue Therapy

At Week 16, subjects classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) will add or modify doses of non-biologic DMARDs, NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), oral corticosteroids, and/or

receive 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroid injection for 1 peripheral joint, 1 trigger point, 1 tender point, 1 bursa, or 1 enthesis. Doses of non-biologic DMARDs and oral corticosteroids may not exceed maximums defined in inclusion criteria (Section 5.2.1).

Corticosteroid injections should be avoided within 21 days prior to the next scheduled study visit to avoid confounding effects of systemic absorption of intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids. For the analysis of the TJC, SJC, and enthesitis sites, injected joints or enthesitis sites will be considered "not assessable" for 90 days from the time of the injection.

5.2.4 Contraception Recommendations

Contraception Recommendation for Females

A woman who is postmenopausal or permanently surgically sterile is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Surgically sterile is defined as:

- bilateral oophorectomy (surgical removal of both ovaries); or
- bilateral salpingectomy (surgical removal of both fallopian tubes); or
- hysterectomy (surgical removal of uterus)

Postmenopausal is defined as:

- Age ≥ 55 years with no menses for 12 or more months without an alternative medical cause;

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

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

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

For a female subject at any age:

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

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

- Combined (estrogen and progestogen containing) hormonal contraception (oral, injectable, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Bilateral tubal occlusion/ligation (Japan only: bilateral tubal ligation only).

- Vasectomized partner(s) provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence, for example, using calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable.

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the 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, contraceptive measures as defined above are no longer required.

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapy. Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.

Additional local requirements may apply. Refer to Appendix G for local requirements.

Contraception Recommendation for Males

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

No contraception is required for male subjects.

If a pregnancy occurs, a partner authorization form requesting pregnancy outcome information may be requested from the pregnant partner.

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

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

Subjects will be allowed a visit window of ± 3 days for all study visits (with the exception of the Baseline Visit, as the screening window is a maximum of 35 days) up to the Week 36 visit. Visits after the Week 36 visit will have a visit window of ± 7 days.

If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline Visit).

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

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

Informed Consent

At the Screening visit, the subject will sign and date a study specific, IEC/IRB approved, informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Separate written consent will be required for each subject in order to participate in the optional exploratory research and validation studies. The separate written consent may be part of the main

consent form. Subjects can withdraw informed consent at any time. Details regarding how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

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

Medical/Surgical History

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

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

Vital Signs, Weight and Height

Vital sign determinations of systolic and diastolic blood pressure, pulse rate (counted for at least 30 seconds after 5 minutes in sitting position), respiratory rate, body weight, and body temperature will be obtained at the designated study visits in Appendix C. Vital signs should be performed before blood draws and prior to receipt of study drug. Height will be measured at the Screening Visit only (with shoes off). All measurements will be recorded in metric units where applicable.

Due to a state of emergency or pandemic situation, subject visits may be conducted via phone or video conference. In these situations, vital signs, and weight may be performed by the subject or caregiver as needed.

Physical Exam

A complete physical examination will be performed at the designated study visits as specified in Appendix C. 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 the Baseline Visit prior to the first dose of study drug should be recorded in the subject's medical history. Abnormalities noted after the Baseline Visit and first dose of study drug should be evaluated and documented by the Investigator as to whether or not these are AEs. All findings whether related to an AE or part of each subject's medical history should be captured on the appropriate eCRF page.

A symptom-directed physical examination will be performed when necessary.

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

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at the Screening Visit and Week 56. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. ECGs with QT interval corrected for heart rate using Friedericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed. In these cases, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. 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 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 all protocol required documentation is available and nothing has changed in the subject's health status since the time of the test that warrants a repeat test. If there are clinically significant findings, 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.

X-Rays of the Hands and Feet

If Item 5 of the CASPAR (Appendix F) criteria needs to be verified for a subject to meet eligibility, prior x-rays (no time limit) of any combination of bilateral hands and feet with images and/or report available to the site can be used to document juxta-articular new bone formation. There is no need to have a full set of x-rays of both hands and both feet as a single image could fulfill this criterion.

If no prior x-rays (images and/or report) are available, subjects are required to have x-rays of both hands and feet at screening in order to document all items of the CASPAR criteria.

If prior x-rays are available, but do not demonstrate radiographic evidence of juxta-articular new bone formation, subjects may have repeat x-rays of both hands and feet at screening if at least 12 weeks has passed since the prior exam.

The Investigator or their qualified delegate should read the x-rays of the hands and feet. It is the responsibility of the Investigator to ensure that all delegates are qualified and that all training is documented.

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

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

A radiologist or pulmonologist must perform an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR (review of images required), a radiologist, the Principal Investigator or their physician 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.

In the event CXR may not be performed at the planned visit due to a state of emergency or pandemic situation, perform the CXR at the next feasible visit.

Pregnancy Test

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

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

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

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

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

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

At each visit, the study staff should review the pregnancy avoidance recommendations with each subject of childbearing potential and 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 in this study or be allowed to continue study drug.

TB Testing/TB Prophylaxis

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

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 QuantiFERON-TB Gold test. The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines). The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF. The TB risk assessment form will be completed annually for all subjects, regardless of TB test results. One or more "yes" response on the TB risk assessment form indicates increased risk of TB. At annual evaluations, questions on the TB risk assessment form should be answered considering the previous year when the timeframe is not indicated in the question.

If a QuantiFERON-TB Gold Test cannot be performed by the Central Lab at Screening and a subject had a negative PPD test within 90 days prior to Screening and source

documentation is available, TB testing by PPD Skin Test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie Therapeutic Area Medical Director. The results of the TB test(s) will be retained at the site as the original source documentation.

In cases where the QuantiFERON-TB Gold test by the central laboratory is positive and the investigator considers the subject at low risk for TB (i.e., no risk factors identified on the TB risk questionnaire) and has no clinical suspicion of TB, the investigator may perform a local QuantiFERON-TB Gold test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive, the test is considered positive.

For subjects with a negative TB test result at Screening or most recent evaluation, an annual TB re-test will be performed. If an annual TB test is newly positive (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. For subjects with seroconversion on an annual TB test, in the absence of a positive response to any question on the TB risk assessment questionnaire, if a CXR cannot be done due to restrictions because of state of emergency or pandemic situations, the investigator should contact the AbbVie TA MD to determine if the subject may continue on study drug. CXR should be performed as soon as restrictions are lifted at the study site or local hospital/facility. Expert consultation can be considered per Investigator's discretion. Any positive TB screen after the patient has started the study should be reported as an AE of latent TB or active TB (as applicable).

Subjects with documentation of a prior positive result of QuantiFERON-TB Gold Test (or equivalent) or PPD are not required to repeat either test at Screening or during the study and should be considered positive.

TB test:

- For regions that require both PPD and QuantiFERON-TB Gold testing, both will be performed. If either PPD or QuantiFERON-TB Gold are positive, the TB test is considered positive.
- If a site has the capacity to perform both PPD and QuantiFERON-TB Gold tests, and local guidelines require only one test to be performed, then the QuantiFERON-TB Gold is the preferred test. At a site with capacity to perform both tests, 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 QuantiFERON-TB Gold test.
- If the QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD Skin Test are required per local guidelines): the PPD Skin Test (also known as a TB Skin Test) will be performed according to standard clinical practice. The TB Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm 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 the TB Skin Test should be considered positive.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the patient is considered to be negative.
- An equivalent Interferon Gamma Release Assay (IGRA) (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold.

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

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

TB prophylaxis:

At screening, if the subject has evidence of latent TB infection (positive TB test and the subject has a CXR not suggestive of active TB), prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer); at least 6 months of prophylaxis needs to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug. If the Investigator deems that it is necessary, consultation with a TB expert could be considered.

Of note: Rifampin (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 will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

For subjects with completion of a full course of anti-TB therapy, but insufficient documentation, the investigator should consult with the AbbVie TA MD.

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

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

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

Clinical Laboratory Tests

Blood and urine samples will be obtained for clinical laboratory tests listed in Table 2. Samples will be obtained at the designated study visits in Appendix C.

Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per Investigator's discretion. A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory test results 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 draws should be performed after all clinical assessments and questionnaires and vital sign determinations have been completed but before any study drug administration during a visit.

In cases of state-of emergency or pandemic situations, local laboratories may be used to collect laboratory samples per instructions from AbbVie, as local regulations allow.

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 the specified time points as noted in Appendix C. The central laboratory will be responsible for performing a macroscopic

urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones or blood greater than negative, or glucose greater than normal will be followed-up with a microscopic analysis at the central laboratory.

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

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

A laboratory test value that requires a subject to be discontinued from study drug treatment or requires a subject to receive treatment will be recorded as an AE. The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

Table 2. Clinical Laboratory Tests

Hematology (Central Lab)	**Clinical Chemistry[a] (Central Lab)**	**Urinalysis[b] (Central Lab)**	**Other Laboratory Tests**
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count	BUN Creatinine Total bilirubin INR (reflex only)[c] Albumin AST ALT Alkaline phosphatase CPK Sodium Potassium Bicarbonate/CO^2 Chloride Calcium Inorganic phosphate Uric acid Total protein Glucose Cholesterol LDL-C HDL-C Triglycerides Advanced lipid testing[d]	Specific gravity Ketones pH Protein Glucose Blood Urobilinogen Bilirubin Leukocytes Nitrites Microscopic examination, if needed	<u>Central Lab Tests:</u> Serum Pregnancy (bHCG) test[e] HBsAg[f] HBsAb[f] HBcAb[f] HBV DNA PCR reflex only[f] HCV Ab[f] HCV RNA reflex only[f] Rheumatoid Factor[f] Anti-CCP antibodies[f] QuantiFERON-TB Gold[g] hs-CRP[h] FSHi[i] beta-D-glucan[j] HIV Ab[k] <u>Local Lab Tests:</u> Urine pregnancy test[l] ESR Varicella antibody, if indicated B cells, if indicated

a. Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

b. A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

c. INR will only be measured if ALT and/or AST > 3 × ULN. A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST.

d. Samples for advanced lipid testing may be stored for batch testing and may include Apo A1, Apo B, and/or other lipid particle tests.

e. A serum pregnancy test will be performed for all female subjects of childbearing potential at the Screening Visit and if post-baseline urine pregnancy is positive.

Table 2. Clinical Laboratory Tests (Continued)

f. At Screening only. For Japan or where mandated by local requirements: for subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening, the HBV-DNA PCR test should be performed again approximately every 12 weeks. Retesting every 12 weeks is not necessary with subjects that have a history of HBV vaccine and is HBs Ab+ and HBc Ab–.

g. All subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix E) and tested for TB infection by QuantiFERON-TB Gold test analyzed by the central laboratory. The PPD Skin Test should be utilized only when an IGRA is not possible for any reason (unless both tests are required per local guidelines).

h. Starting from Baseline (Day 1) the hs-CRP results will not be reported to the Sponsor, Investigator, study site personnel, or the subject. For safety evaluations of signs and symptoms of infection and management of adverse events, the investigator may locally test procalcitonin. Results of tests such as hs-CRP, 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. Any local hs-CRP, CRP, or serial procalcitonin tests reported to the investigator until a subject is known to receive upadacitinib or until treatment allocation is unblinded will be recorded as protocol deviations.

i. At screening for female subjects < 55 years of age AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization.

j. Japan only. If the result from the central lab is indeterminate or otherwise not interpretable, a local lab may be used.

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

l. A urine pregnancy test will be performed for all female subjects at the Baseline Visit prior to the first dose of study drug and all subsequent visits. If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from study drug treatment. In the event a serum pregnancy test comes back borderline, a repeat test is required ≥ 3 days later to document continued lack of a positive result. If a urine pregnancy test post-baseline is positive, study drug must 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.

HIV Test

Subjects with HIV infection are excluded from study participation. HIV antibody (Ab) testing will be performed at Screening. The Investigator must discuss any local reporting

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

Hepatitis Screening

All subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening.

Hepatitis B:

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

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

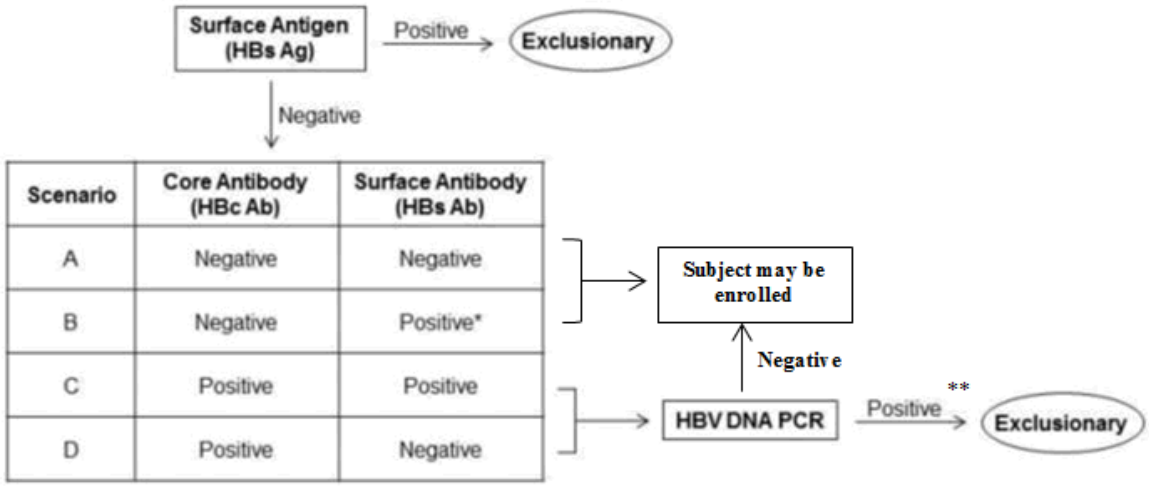
A positive result for HBs Ag will be exclusionary.

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

- A negative test result for HBc Ab does **not** require HBV DNA PCR qualitative testing and the subject may be enrolled (Figure 2, Scenarios A and B).
- For a subject who has had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected, the HBV DNA PCR qualitative testing is **not** required and the subject may be enrolled. For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab requires HBV DNA PCR testing (automatic reflex testing). Figure 2, Scenario B.

- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 2, Scenarios C and D).
- A positive result for HBV DNA or a result that exceeds detection sensitivity will be considered positive and will be exclusionary. A subject with a negative result for HBV DNA may be enrolled.
- For Japan or where mandated by local requirements: subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed approximately every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–. If necessary, HBV DNA PCR may be tested at unscheduled visits.

Figure 2. Interpretation and Management of HBV Serologic Test Results



* For subjects who have had a HBV vaccination (should be documented in the medical history), a positive test result for HBs Ab is expected and these subjects may be enrolled. For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab requires HBV DNA PCR testing.

** For Japan or where mandated by local requirements: subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening should have HBV DNA PCR testing performed approximately every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–. If necessary, HBV DNA PCR may be tested at unscheduled visits.

Hepatitis C:

All subjects will be tested for the presence of Hepatitis C Virus antibodies (HCV Ab) at Screening. Samples positive for HCV Ab require PCR qualitative testing for HCV RNA. Any HCV RNA PCR result that meets or exceeds detection sensitivity will be exclusionary. Subjects with a history of treated HCV infection may be allowed to enroll if documentation of effective treatment is available and no evidence of HCV is detected by HCV RNA PCR.

Randomization and Drug Assignment

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

Subjects will be eligible for randomization if they continue to meet all of the selection criteria (Section 5.2) at the Baseline Visit and are willing to continue in the study. Subjects will be randomized in a 2:2:1:1 ratio using an Interactive Response Technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: upadacitinib 15 mg QD (N = 210)
- Group 2: upadacitinib 30 mg QD (N = 210)
- Group 3: Placebo followed by upadacitinib 15 mg QD (N = 105)
- Group 4: Placebo followed by upadacitinib 30 mg QD (N = 105)

No more than approximately 40% of subjects will be enrolled with < 3% BSA extent of psoriasis and no more than approximately 30% of subjects will be enrolled with prior failure of more than 1 biologic DMARD.

Randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, and number of prior failed (had an inadequate response to) biologic DMARDs (1 vs >1), except for subjects from Japan, for

which randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA) only. See Section 5.5.3 for details.

Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

Study Drug Dispensing, Dosing, and Compliance

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

In cases of state-of emergency or pandemic situations, study drug may be shipped directly to subjects per instructions from AbbVie, as local regulations allow.

All relevant dosing information will be entered into the eCRF at each visit. (Refer to Section 5.5 for additional information).

Subject Diary

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

Patient Questionnaires

Subjects will complete the following questionnaires as specified in Appendix C. A validated translation will be provided in their local language, as applicable:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- EuroQol-5D-5L (EQ-5D-5L) Health Questionnaire
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- Disability Index of the Health Assessment Questionnaire (HAQ-DI)
- Patient's Assessment of Pain Numeric Rating Scale (0 – 10 NRS)
- Patient's Global Assessment (PtGA) of Disease Activity Numeric Rating Scale (0 – 10 NRS)
- Self-Assessment of Psoriasis Symptoms (SAPS)
- SF-36 Health Questionnaire
- Work Productivity and Activity Impairment (WPAI)

All patient-reported outcomes (PROs) are 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.

In cases of state-of emergency or pandemic situations, PROs may be administered on paper or over the telephone directly to subjects by site personnel within the study visit window per instructions from AbbVie, as local regulations allow.

Investigator Assessments

The investigator assessments will be recorded on paper worksheets and entered into the eCRF and conducted at the study visits specified in Appendix C. For the following assessments, if possible, the investigator assessments should be performed by an independent and blinded assessor who should not perform any other study related procedures.

- Psoriasis Area Severity Index (PASI)
- Body Surface Area (BSA)
- Static Investigator Global Assessment (sIGA)
- TJC and SJC Assessment
- Dactylitis
- Enthesitis

In order to minimize variability, the same assessor should evaluate the subject at each visit for the duration of the trial. A back-up assessor should be identified. The assessor should be a qualified medical professional (e.g., nurse, physician's assistant, or physician) or be pre-approved by the TA MD as an assessor after review of assessor training and experience. Any 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 assessments and that all training is documented. If the assessor is not available, the pre-identified back-up assessor should perform such assessments.

Physician's Global Assessment (PGA) of Disease Activity Numerical Rating Scale (NRS)

The PGA-Disease Activity will be conducted to assess the subject's current disease activity, taking into consideration both arthritis and psoriasis activity, independent of the subject's self-assessment, using a 0 – 10 NRS, anchored at either end by opposite adjectives.

The assessor is not required to be independent but should be a qualified medical professional, preferably a physician.

Health Resource Utilization (HRU) Questionnaire

Sites will complete a HRU questionnaire at the study visits specified in Appendix C. The questionnaire will be interview administered by the site. The assessor is not required to be independent and may be a qualified medical professional or a study coordinator. The answers will be completed on the source worksheet provided by the sponsor and entered in the eCRF.

Psoriasis Assessments

Psoriasis Area Severity Index (PASI)[47]

The PASI is a measure of psoriasis severity. Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration and desquamation using a 5-point scale. Based on the extent of lesions in a given anatomic site, the area affected is assigned a numerical value.

Since the head, upper extremities, trunk and lower extremities correspond to approximately 10, 20, 30 and 40% of body surface area, respectively; the PASI score is calculated using the formula:

1. $PASI = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$

Where *E, I, D*, and A denote erythema, induration, desquamation, and area, respectively, and *h, u, t*, and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest possible degree.

Typically scores of 3 or less represent mild disease, scores over 3 and up and including 15 represent moderate disease and scores over 15 are considered to be associated with severe disease.

The assessor should be an independent qualified medical professional.

Body Surface Area (BSA) – Psoriasis

The subject's right or left hand should be selected as the measuring device. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1%. Measurement of the total area of involvement is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved.

The assessor should be an independent qualified medical professional.

Static Investigator Global Assessment (sIGA)

The sIGA is a 5 point score ranging from 0 to 4, based on the investigator's assessment of the average elevation, erythema, and scaling of all psoriatic lesions.

The assessment is considered "static" which refers to the patients disease state at the time of the assessments, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit.

A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

The assessor should be an independent qualified medical professional.

TJC and SJC Assessment

TJC Assessment

An assessment of 68 joints will be done for tenderness by pressure manipulation on physical examination. Joint pain/tenderness will be classified as: present, absent or no assessment. Joints injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The assessor should be an independent qualified medical professional.

SJC Assessment

An assessment of 66 joints will be done by directed physical examination. 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, absent, replaced or no assessment. Joints injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The assessor should be an independent qualified medical professional.

Dactylitis

Leeds Dactylitis Index (LDI[47])

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

The assessor should be an independent qualified medical professional.

Enthesitis

Leeds Enthesitis Index (LEI)

This evaluation will be conducted to assess the presence or absence of enthesitis at 3 bilateral sites. Tenderness on examination is recorded as either present, absent, or not assessed for each of the 6 sites, for an overall score range of 0 – 6. Enthesitis sites injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The assessor should be an independent qualified medical professional.

Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index

This evaluation will be conducted to assess the presence or absence of enthesitis at 9 bilateral sites. Tenderness on examination is recorded as either present, absent, or not assessed for each of the 18 sites. For scoring purposes, the inferior patella and tibial tuberosity are considered to be one site due to their anatomical proximity the overall score range is 0 – 16. Enthesitis sites injected with corticosteroid will be considered non-evaluable for 90 days from the time of the injection.

The Lateral epicondyle and Achilles tendon insertion will only need to be assessed once since the 2 bilateral sites overlap between the LEI and SPARCC.

The assessor should be an independent qualified medical professional.

Psoriatic Spondylitis

This evaluation will be conducted at Baseline only as a single question asking the investigator to take into consideration all that is known about the subject to assess whether or not the subject has psoriatic spondylitis. Responses will be recorded as yes or no. This evaluation should be assessed by the rheumatologist investigator.

5.3.1.2 Optional Samples for Exploratory Research and Validation Studies

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

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 PsA by assessing associations between disease characteristics, outcomes data and biomarkers of interests.

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.

For Japan only: The research on DNA and RNA exploratory research samples will be restricted to the subject's response to the 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 PsA and related conditions continues, but for no longer than 20 years after study completion.

All subjects are preferred to have been fasting for a minimum of 8 hours prior to sample collection. 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. The following samples will be collected according to Appendix D for each subject who consents to provide samples for exploratory research/validation studies:

- DNA samples for pharmacogenetic or epigenetic analyses
- RNA samples for transcriptomic and/or epigenetic analyses
- Serum and plasma samples for systemic analyses, including but not limited to proteomic and metabolomics
- Urine samples for investigations including, but not limited to, targeted protein and metabolomic analyses

The procedures for obtaining and documenting informed consent are discussed in Section 9.3.

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

5.3.2 Drug Concentration Measurements

Blood Samples for upadacitinib PK Assay (Period 1 Only)

Blood samples (plasma) for assay of upadacitinib and possibly other medications will be collected as follows (Appendix C):

- Weeks 2 and 4 prior to dosing;
- Weeks 8 and beyond at any time during the visit. For subjects who prematurely discontinue from study drug treatment prior to Week 56, at any time during the PD visit.

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

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

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

5.3.2.1 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Primary Variables

The primary efficacy 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 TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain (NRS), PtGA of Disease Activity (NRS), PGA of Disease Activity (NRS), HAQ-DI, or hs-CRP.

5.3.3.2 Key Secondary Variables

The key multiplicity adjusted secondary efficacy endpoints (each dose of upadacitinib versus placebo) are:

1. Change from baseline in HAQ-DI at Week 12;
2. Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16;
3. Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with ≥ 3% BSA psoriasis at baseline);
4. Change from baseline in SF-36 PCS at Week 12;
5. Change from baseline in FACIT-Fatigue Questionnaire at Week 12;
6. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
7. Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16.

Additional key secondary efficacy endpoints (each dose of upadacitinib versus placebo) are:

- ACR50/70 response at Week 12;
- ACR20 response at Week 2.

ACR20/50/70 response rates will be determined based on 20%/50%/70% or greater improvement in TJC and SJC and ≥ 3 of the 5 measures of Patient's Assessment of Pain NRS, PtGA of Disease Activity NRS, PGA of Disease Activity NRS, HAQ-DI, or hs-CRP.

The proportion of subjects achieving MDA[14] will be determined based on subjects fulfilling 5 of 7 outcome measures: TJC ≤ 1; SJC ≤ 1; PASI ≤ 1 or BSA-Ps ≤ 3%; patient assessment of pain ≤ 1.5 (0 – 10 NRS); PtGA-disease activity ≤ 2 (0 – 10 NRS); HAQ-DI score ≤ 0.5; and tender entheseal points ≤ 1.

5.3.3.3 Additional Variables

The following outcome measures will be assessed when obtained at the scheduled time points in Appendix C other than those specified for the primary and key secondary variables:

- Change from baseline in individual components of ACR response;
  - Change from baseline in Tender Joint Count (TJC) (0 – 68);
  - Change from baseline in Swollen Joint Count (SJC) (0 – 66);
  - Change from baseline in Physician Global Assessment (PGA) – Disease Activity (NRS);
  - Change from baseline in Patient's Global Assessment (PtGA) – Disease Activity (NRS);
  - Change from baseline in Patient's Assessment of Pain Numerical Rating Scale (NRS);
  - Change from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI);

  - Change from baseline in High-Sensitivity C Reactive Protein (hs-CRP);
- ACR 20/50/70 response rates;
- Change from baseline in Leeds Dactylitis Index (LDI);
- Change from baseline in dactylitis count;
- Proportion of subjects with resolution of dactylitis;
- Change from baseline in LEI;
- Proportion of subjects with resolution of enthesitis sites included in the LEI;
- Change from baseline in SPARCC Enthesitis Index;
- Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index;
- Change from baseline in total enthesitis count;
- Proportion of subjects with resolution of enthesitis;
- PASI 75/90/100 response rates (for subjects with ≥ 3% Body Surface Area (BSA) psoriasis at baseline);
- Proportion of subjects achieving a static Investigator Global Assessment of psoriasis (sIGA) score of 0 or 1 and at least a 2-point improvement from baseline;
- BSA-Ps;
- Modified Psoriatic Arthritis Response Criteria (PsARC) response rate;
- Change from baseline in Disease Activity Score 28 (DAS28) (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in PsA Disease Activity Score (PASDAS);
- Change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) score;
- Change from baseline in Short Form 36 (SF-36) Health Questionnaire;
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire;
- Change from baseline in EuroQol-5D-5L (EQ-5D-5L) Questionnaire;
- Change from baseline in Work Productivity and Activity Impairment (WPAI) Questionnaire;

- Health Resource Utilization (HRU);
- Proportion of subjects achieving MDA;
- Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire;
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);
- BASDAI 50 response rates;
- Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6);
- Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS);
- Proportion of subjects with ASDAS Inactive Disease;
- Proportion of subjects with ASDAS Major Improvement;
- Proportion of subjects with ASDAS Clinically Important Improvement.
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35).

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

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

5.3.6 Exploratory Research and Validation Studies Variables

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.

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

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 PsA or related conditions and/or upadacitinib or drugs of similar classes. The results from these analyses are exploratory in nature and may not be included with the study report.

The samples may also be used to develop new therapies, research methods or technologies. In addition, samples from this study may be banked for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time and for any reason. The Investigator may discontinue any subject's participation for any reason, including an AE, safety concerns or failure to comply with the protocol. See Section 6.1.7 for toxicity management criteria. Subjects will be withdrawn from study drug treatment immediately if any one of the following occurs:

- Clinically significant abnormal laboratory result(s) or AE(s), 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 study drug or the study
- Inclusion and 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 or AbbVie TA MD
- Subject develops a gastrointestinal perforation, defined as acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention (other than appendicitis or mechanical injury).
- Subjects with disease progression or not responding to treatment are to be withdrawn from study drug treatment based on investigator's discretion
- Starting at Week 36, subjects who fail to show at least 20% improvement in either or both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.

In order to minimize missing data for safety and efficacy assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits as outlined in Appendix C, and adhere to all study procedures except for dispensing study drug, annual TB testing, PK sample collection, and blood sample collection for optional exploratory research and validation studies, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent). In addition, all future rescue and efficacy driven discontinuation criteria no longer apply. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject is discontinued from study drug, the procedures outlined for the PD Visit should be completed as soon as possible, preferably within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. In addition, if subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) after the last dose of study drug may be completed to determine the status of any ongoing AEs/SAEs, the occurrence of any new AEs/SAEs, and medications used to treat AEs/SAEs. Subjects who discontinue the study prematurely after randomization will not be replaced.

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

Lost to Follow-Up

For subjects that are 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 documents.

5.4.2 Discontinuation of Entire Study

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

5.5 Treatments

5.5.1 Treatments Administered

There is one active study drug in this study: upadacitinib.

Upadacitinib (or matching placebo) 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 background non-biologic DMARD therapy. AbbVie will not supply background DMARDs.

When the last subject completes the Week 56 visit, study drug assignment in both periods will be unblinded to the sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit.

5.5.2 Identity of Investigational Product(s)

The individual study drug information is presented in Table 3.

Table 3. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib (ABT-494)	Oral	Tablet	15 mg 30 mg	AbbVie
Upadacitinib (ABT-494) Matching Placebo	Oral	Tablet	NA	AbbVie

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 Drug(s)

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 meeting eligibility criteria will be centrally randomized using an IRT system. Before the study is initiated, IRT directions will be provided to each site.

At the Screening Visit, subjects will be assigned a unique subject number by the IRT. The unique subject number will be used for each subject throughout the study. 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 who meet the inclusion and exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized in a 2:2:1:1 ratio to one of four treatment groups at Baseline (Day 1) as follows:

- Group 1: upadacitinib 15 mg QD (N = 210)
- Group 2: upadacitinib 30 mg QD (N = 210)
- Group 3: Placebo followed by upadacitinib 15 mg QD (N = 105)
- Group 4: Placebo followed by upadacitinib 30 mg QD (N = 105)

No more than approximately 40% of subjects will be enrolled with < 3% BSA extent of psoriasis and no more than approximately 30% of subjects will be enrolled with prior failure of more than 1 biologic DMARD.

Subjects will receive oral study drug QD (upadacitinib 15 mg, upadacitinib 30 mg, or matching placebo) until the end of the study or they discontinue study drug.

Randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, and number of prior failed (had an inadequate response to) biologic DMARDs (1 vs > 1), except for subjects from Japan, for which randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA) only.

The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the Data Sciences and Statistics Departments 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 drugs 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 regarding Week 2 and Week 4 visits).

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

Upadacitinib/Placebo (daily dosing):

- If a subject should forget to take their upadacitinib (or matching placebo) dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.
- If the subject experiences a study drug interruption > 14 consecutive days during the first 24 weeks or > 21 consecutive days after Week 24, they should notify their study site physician, and the subject should be discontinued from study drug treatment.

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/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 (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/helpdesk/.

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.

When the last subject completes the last visit of Period 1 (Week 56), study drug assignment in both periods will be unblinded to the sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

5.5.5.2 Blinding of Data for Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) comprised of persons external to AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. If necessary to ensure subject safety, the DMC will also be given access to selected efficacy data which will be specified in the DMC charter. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A DMC charter will be prepared for the safety data review 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 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 in the IRT that study drug supplies are received intact and in the correct amounts.

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

All empty/used study drug packaging will be inventoried by the site. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary. Site staff will complete study drug accountability via IRT, source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible.

After drug accountability has been completed by the site, empty used packaging may be discarded with any subject identifiers removed or returned to AbbVie-designated destruction depot.

Unused study drug and used packaging with remaining study drug will be destroyed on site according to local procedures or regulations or returned to the AbbVie-designated destruction depot (for those sites that do not meet AbbVie's documentation requirements for on-site destruction).

For sites performing on-site drug destruction or using a third party vendor for drug destruction a copy of the destruction methodology and date of destruction/date prepared for destruction should be maintained at the site's facility. Monitors will reconcile the site's process, source documents, subject's dosing diaries, IRT or site accountability records, and destruction records to assure site compliance.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This study includes two periods.

Period 1 is 56-weeks in duration and includes a 24 week randomized, double-blind, parallel-group, placebo-controlled period followed by an additional 32 weeks of blinded treatment (Weeks 24 – 56). Period 1 is designed to compare the safety, tolerability and efficacy of upadacitinib 15 mg QD and 30 mg QD versus placebo subjects with moderately to severely active PsA and have an inadequate response to biologic DMARDs (Bio-IR). Period 1 is designed to test the superiority of upadacitinib versus placebo for achieving the primary endpoint (ACR20 at Week 12) and other efficacy parameters at Weeks 12 – 24. At Week 24 all subjects will be given upadacitinib and will continue on blinded treatment until all subjects have completed the last visit of Period 1 (Week 56). This will allow unbiased assessments of long-term safety of upadacitinib without compromising the study conduct or results of the ongoing study. In addition, the blinded

study design will allow the assessment of the maintenance of treatment response of both doses in an unbiased manner during the first year of the study.

The purpose of Period 2 is to further evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in PsA subjects who have completed Period 1. All subjects will continue treatment to which they were assigned at the end of Period 1 in an unblinded manner.

When the last subject completes the last visit of Period 1 (Week 56), study drug assignment will be unblinded to the sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical and laboratory procedures will be utilized in this study. Efficacy measurements in this study have been selected or designed to assess disease activity in subjects with PsA. Other than the biomarker analyses which are exploratory, 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 PsA patients who have had an inadequate response to prior bDMARD treatment. Key entry criteria are to enroll adult female and male subjects who are at least 18 years of age with a clinical diagnosis of PsA and who fulfill the CASPAR classification criteria with symptoms for at least 6 months. Eligible study subjects must have ≥ 3 swollen joints (based on 66 joint counts) and ≥ 3 tender joints (based on 68 joint counts) at Screening and Baseline Visits.

5.6.4 Selection of Doses in the Study

The doses of upadacitinib selected for this study 15 mg QD and 30 mg QD dosed up to approximately 3 years, are expected to be efficacious with an acceptable safety profile. Two doses of upadacitinib have been selected for this study in order to perform limited dose ranging in subjects with PsA. The upadacitinib 15 mg QD and 30 mg QD doses

were selected as they are expected to demonstrate efficacy in the treatment of patients with PsA while limiting potential drug-related effects on laboratory parameters (e.g., hemoglobin). Doses of 15 mg QD and 30 mg QD are the doses that are currently being evaluated in Phase 3 trials in rheumatoid arthritis (RA). The doses being evaluated in the RA Phase 3 trials are considered appropriate for investigation in PsA as (1) effects of upadacitinib on tender and swollen joints, markers of inflammation, and ACR responses are expected to be similar in RA and PsA; and (2) proof of concept has been demonstrated with another JAK inhibitor (tofacitanib) at the doses that are efficacious in RA. In addition, in RA the plateau for efficacy was achieved by exposures equivalent to 30 mg QD, indicating that higher doses may not provide greater therapeutic benefit.

Results from two Phase 2b trials in subjects with RA with the upadacitinib immediate-release capsule formulation indicate that all evaluated doses (3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID, and 24 mg QD) were generally well tolerated and without unexpected safety concerns. The Phase 2 dose-response and exposure-response results in RA show that the 6 mg BID dose approaches the plateau of efficacy, and increasing the dose to 12 mg BID appears to result in some incremental efficacy benefit, particularly in the more refractory subjects with inadequate response or intolerance to anti-TNF biologic therapy. Therefore, upadacitinib exposures associated with 6 mg BID and 12 mg BID were selected as the target exposures to evaluate in Phase 3 trials in RA.

In order to enhance patients' compliance and to provide a more convenient dosing regimen than BID administration, AbbVie developed a once-daily tablet formulation which will be used in the current study.

A bioavailability study has demonstrated that 15 mg QD and 30 mg QD regimens of the once-daily tablet formulation provide equivalent daily AUC and comparable C_{max}, and C_{min} to 6 mg BID and 12 mg BID, respectively, of the immediate-release capsule formulation used in Phase 2 studies in RA.

The mean exposures (AUC and C_{max}) for the highest dose that will be evaluated in this study (30 mg QD) are predicted to be lower than the exposures associated with the

no-observed-adverse-effect level in the 9-month GLP preclinical toxicology study in dogs (1.5 mg/kg/day) and lower than the highest mean upadacitinib exposures evaluated in healthy subjects or in patients in previous clinical studies.

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 adverse events (AE), please refer to Sections 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 serious adverse events (SAE) considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

Expected manifestations of PsA (i.e., psoriasis, joint pain and swelling, dactylitis, enthesitis, etc.) are not to be recorded as AEs unless the manifestation is considered to be a disease flare (worsening) of the underlying condition.

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

6.1.1.2 Serious Adverse Events

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

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

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

6.1.1.3 Adverse Events of Special Interest

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

- Serious infections;
- Opportunistic infections;
- Malignancy (all types);
- Hepatic disorder;
- Gastrointestinal Perforations;
- Anemia;
- Neutropenia;
- Lymphopenia;
- Herpes Zoster;
- Creatine Phosphokinase (CPK) elevation;
- Renal dysfunction;
- Tuberculosis;
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Embolic and thrombotic events (non-cardiac, non-CNS)

6.1.2 Adverse Event Severity

When criteria are available, events should be graded as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc. If guidance for specific events is not available grading should be as follows:

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

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

Severe (Grade 3 – 5):

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
- Grade 4: Life-threatening consequences; urgent intervention indicated;
- Grade 5: Death related to AE.

6.1.3 Relationship to Study Drug

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

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

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

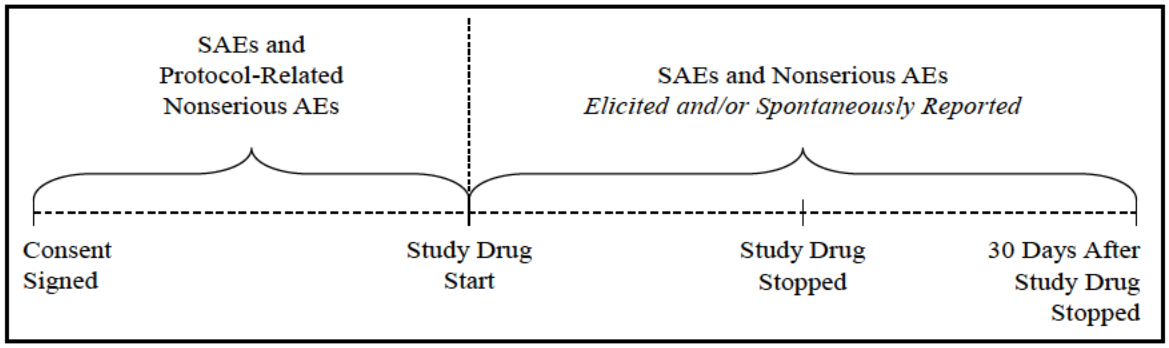
If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the serious adverse event.

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

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



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

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

- Cardiac events;

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

In the case of a reported AE of herpes zoster infection or a non-cardiac, non-CNS embolic or thrombotic event, or is COVID-19 related a Supplemental AE eCRF should be completed.

6.1.5 Serious Adverse Event Reporting and Malignancy Reporting

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

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

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

Phone: +1 (833) 942-2276
Email: SafetyManagement_Immunology@abbvie.com

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

Therapeutic Area Medical Director (TA MD):

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

Phone:
Mobile:
Email: [redacted]

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

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for upadacitinib.

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 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study drug treatment (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. Pregnancies in study subjects and female partners of male subjects 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. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

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

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

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Re-challenge with study drug may occur once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug. See Section 5.5.4 Selection and Timing of Dose for Each Subject for study drug interruption guidelines.

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

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a gastrointestinal perforation should be evaluated promptly for early diagnosis and treatment. Gastrointestinal perforation is defined as acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention. If the diagnosis of gastrointestinal perforation is confirmed (other than due to appendicitis or mechanical injury), the subject must be discontinued from study drug.

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

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

Muscle-related symptoms: If a subject experiences symptoms suggestive of myositis or rhabdomyolysis, consider checking CPK and aldolase with clinical management and/or study drug interruption as deemed appropriate by the treating physician.

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

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

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

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 4 and may require an appropriate supplemental eCRF be completed. For subjects with ongoing laboratory abnormalities which require data entry into an eCRF, an additional eCRF related to subsequent laboratory abnormalities is only required if the subject has relevant changes in history (e.g., new onset signs or symptoms) or laboratory values which have returned to normal reference range or its Baseline value followed by subsequent laboratory abnormalities meeting toxicity guidelines (considered a new event). All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 4, the repeat testing must occur as soon as possible.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline and an alternative etiology is known or the hemoglobin value remains in the normal reference range, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its Baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1000/μL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Interrupt study drug if confirmed < 500/μL by repeat testing with new sample. If value returns to normal reference range or its Baseline value, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason that rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
Absolute lymphocyte counts (ALC)	• If confirmed < 500/μL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total white blood cell count	• If confirmed < 2000/μL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its Baseline value.
Platelet count	• If confirmed < 50,000/μL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its Baseline value.

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

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5. o A separate blood sample for INR testing will be needed to measure INR at time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from Baseline). • If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with new sample, and contact the TA MD. • Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA PCR testing performed within 1 week (based on initial elevated value): o ALT > 5 × ULN OR o ALT or AST > 3 × ULN if an alternative cause is not readily identified. • A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST. A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.

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

Laboratory Parameter	Toxicity Management Guideline
AST or ALT (Continued)	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).
Serum Creatinine	• If serum creatinine is > 1.5 × the Baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × Baseline value and ≤ ULN. • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete the appropriate supplemental renal eCRF(s).
Creatine Phosphokinase	• If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If confirmed CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. For the above CPK elevation scenarios, complete supplemental CPK eCRF.

For study drug interruption, the following rules apply:

- During first 24 weeks, study drug interruption of ≤ 14 consecutive days is allowed.
- After Week 24, study drug interruption of ≤ 21 consecutive days is allowed.
- If the subject must undergo emergency surgery, the study drugs should be interrupted at the time of the surgery.

- Elective surgery during the first 24 weeks is not allowed.
- Elective surgery between Weeks 24 and 56 is discouraged and should be discussed with the AbbVie TA MD.
- If the subject undergoes elective surgery, the study drugs should be interrupted 1 week prior to the planned surgery.
- After surgery, allow reintroduction of study drug once a 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 and Trial Monitoring Committee

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

6.1.9 Cardiovascular Adjudication Committee

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

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

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

Primary Contact:

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

Office:
Fax:
Email: [redacted]

Alternate Contact:

[redacted]
AbbVie s.r.l.
Viale dell' Arte, 25
00144 Rome
ITALY

Office:
Mobile:
Email: [redacted]

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

Examples of protocol deviations include the following:

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

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 Week 24 or have prematurely discontinued for the purpose of initial regulatory submission. To maintain integrity of the trial during the blinded 56-week period, study sites and subjects

will remain blinded until all subjects have reached Week 56. A second unblinded analysis may be conducted for regulatory purposes after all subjects have completed Period 1. A final analysis will be conducted after all subjects have completed Period 2.

Complete 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 first unblinded analysis (Week 24 analysis). The statistical analyses will be performed using a SAS® (SAS Institute Inc., Cary, NC, USA).

Upon approval of protocol amendment 8, subjects receiving upadacitinib 30 mg QD will be switched to upadacitinib 15 mg QD at their next scheduled study visit. The details for handling the change in dose in analysis will be described in the Statistical Analysis Plan (SAP) for final reporting.

8.1.1 Analysis Populations

8.1.1.1 Full Analysis Set (FAS)

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

8.1.1.2 Per Protocol Analysis Set

The Per Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects who did not have major protocol violations which are expected to impact the primary endpoint. Additional analysis may be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol violations. The Per Protocol Analysis Set will be determined prior to the Week 24 analysis.

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 as appropriate: the number of subjects randomized, the number of subjects who received at least one dose of study drug, the number of subjects who completed, and the number of subjects who prematurely discontinued study participation.

8.1.2.2 Subject Disposition

Separately for Period 1 and Period 2, the number and percentage of subjects who are randomized, received at least one dose of study drug, prematurely discontinued study drug, prematurely discontinued study participation, and completed will be summarized by treatment group and overall. Reasons for premature discontinuation of study drug and study participation will be summarized separately for all randomized subjects by treatment group and overall, with frequencies and percentages by reason for discontinuation.

8.1.2.3 Study Drug Exposure

Exposure to study drug will be summarized for the Safety Analysis Set for Period 1 alone as well as for Period 1 and Period 2 combined. The exposure to study drug (days) will be summarized with the mean, standard deviation, median, and range for each treatment group. The exposure to study drug is defined as the difference between the dates of the first and last doses of the oral study drug plus 1 day.

Study drug compliance will be summarized for each treatment group for Period 1. The compliance for oral study drug is defined as the total number of tablets taken divided by the total number of tablets a subject is supposed to take during 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.

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 Primary Efficacy Variable

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

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

8.1.4.2 Key Secondary Efficacy Variables

Unless otherwise specified, comparisons are between each dose group of upadacitinib and the combined placebo group.

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

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons between each upadacitinib dose group and the combined placebo groups will be carried out using Mixed-Effects Model Repeated Measures (MMRM) with fixed effects of treatment group, visit, treatment-by-visit interaction and the baseline measurements.

8.1.4.3 Additional Efficacy Variables

Additional efficacy variables as listed in Section 5.3.3.3 will be summarized for all visits, including visits beyond Week 24. For binary endpoints, frequencies and percentages will be reported by treatment group by visit. For continuous endpoints, the mean, standard deviation, median, and range will be reported by treatment group by visit.

8.1.4.4 Multiplicity Control for the Primary and Key Secondary Endpoints

The overall type I error rate of the primary and key secondary endpoints for the two doses will be strongly controlled using a graphical multiple testing procedure.[48,49] Specifically, the testing will utilize the endpoint sequence of primary endpoint followed by key secondary endpoints in the order as specified in Section 5.3.3.2, and will begin with testing the primary endpoint using two-sided α of 0.025 for each dose. Continued testing

will follow a pre-specified α transfer path which includes downstream transfer along the endpoint sequence within each dose as well as cross-dose transfer. More details of the graphical procedure will be specified in the SAP.

8.1.4.5 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.

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

Mixed Model Repeated Measures (MMRM): The MMRM includes treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline as covariate.

The NRI approach will serve as the primary analysis approach for binary endpoints. Analysis for key binary endpoints will also be repeated using OC. The mixed model repeated measures (MMRM) will serve as the primary analysis for continuous key secondary endpoints. A Missing Not At Random (MNAR) model that varies assumptions for the missing data in active treatment groups and placebo groups may be used as a sensitivity analysis for important continuous endpoints to account for potential deviation from the missing at random assumption.

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

The efficacy variables are listed in Section 5.3.3.3 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. There will be two sets of planned safety analysis: safety analysis by Week 24, and long-term safety analysis.

Safety analyses are based on treatments actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, 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 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 sets of safety analysis.

8.1.5.2.1 Treatment-Emergent Adverse Events (TEAE)

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

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

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

- All AEs

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

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

TEAEs will be summarized and presented by 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 AESIs listed in Section 6.1.1.3 will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the long term safety analysis.

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 and Vital Sign Data

Summary statistics 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 0, Grade 1, Grade 2, Grade 3, and Grade 4 based on National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE). The shift tables will tabulate the number and percentage of subjects with baseline and post-baseline values by the above categories.

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

8.1.6 Pharmacokinetic and Exposure-Response Analyses

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

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

Population PK analyses will be performed using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The CL/F and V/F of upadacitinib will be the PK parameters of major interest in the analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis. The relationship between the conditional estimates of CL/F and V/F values with only potentially physiologically relevant or clinically meaningful

covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic of renal function, etc.) will be explored using stepwise forward selection backward elimination approach. Relationships between upadacitinib exposure and clinical observations will be explored. The effect of meaningful covariates (e.g., body weight) on the exposure-response relationships for efficacy measures (e.g., ACR and PASI) in PsA patients will be evaluated.

Results of the PK and exposure-response analyses may be summarized in a separate report, rather than in the CSR. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The planned sample size of 630 for this study provides at least 90% power for a 20% difference in ACR20 response rate (assuming a placebo ACR20 response rate of 20%). It will also provide at least 90% power for the majority of the key secondary endpoints. All power and sample size calculations are performed at two-sided significance level of 0.025 and accounting for a 10% dropout rate.

8.3 Randomization Methods

Subjects will be randomly assigned in a 2:2:1:1 ratio per study design diagram Figure 1.

Randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD, and number of prior failed (had an inadequate response to) biologic DMARDs (1 vs > 1), except for subjects from Japan, for which randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA) only. See Section 5.5.3 for details.

9.0 Ethics

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

Good Clinical Practice (GCP) 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 ICH GCP.

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

9.2 Ethical Conduct of the Study

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

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

9.3 Subject Information and Consent

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

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

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 IEC/IRB, 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. If the subject does not consent to the exploratory research/validation studies, it will not impact the subject's participation in the study.

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

In cases of state-of emergency or pandemic situations, in addition to the study informed consent additional verbal consent may be obtained prior to adaptations or substantial changes in study conduct, according to local regulations (e.g., labs taken at a local facility, direct to patient courier study drug delivery, home or virtual study visits, etc.).

9.3.1 Informed Consent Form and Explanatory Material

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

9.3.2 Revision of the Consent Form and Explanatory Material

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

the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

In cases of state of emergency or pandemic situations, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

Case report forms (CRF) 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 electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (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.

Supplemental study case report forms should be completed in the event of COVID-19 (coronavirus SARS-CoV-2) related missing/incomplete/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

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.

Electronic Patient Reported Data:

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmanager, provided by the technology vendor Signant Health of

Plymouth Meeting, PA, USA. 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, Signant Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

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

The ePRO data will be collected electronically via a Tablet device into which the patient 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 patients to complete more than one of the same assessments 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 Signant Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

In cases of state-of emergency or pandemic situations, PROs may be administered within the study visit window on paper or over the telephone by site personnel directly to subjects per instructions from AbbVie, as local regulations allow.

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

The assessments completed by the subject will be considered source documentation.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

All information concerning upadacitinib and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of upadacitinib. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any exploratory research/validation studies that may be done using the samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management, hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject 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 exploratory research/validation studies from this study may be used in scientific publications or presented at medical conventions. The data from exploratory research/validation studies will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

The Investigator (Director of the site in Japan) must 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 (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

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

Protocol Title:	A Phase 3, Randomized, Double-Blind, Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Active Psoriatic Arthritis Who Have a History of Inadequate Response to at Least One Biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) – *SELECT – PsA 2*
Protocol Date:	29 January 2021

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Immunology Therapeutic Area
		Immunology Therapeutic Area
		Pharmacovigilance and Patient Safety
		Statistics
		Statistics
		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development

Appendix C. Study Activities

Activity	SCR D –35 to D –1	BL D 1	Wk 2 D 15	Wk 4 D 29	Wk 8 D 57	Wk 12 D 85	Wk 16 D 113	Wk 20 D 141	Wk 24 D 169	Wk 28 D 197	Wk 32 D 225	Wk 36 D 253	Wk 44 D 309	Wk 56 D 393	Wk 68[a] to Wk 140 (Every 12 Wks) D 477 to D 981	Wk 152 or PD D 1065	30 Day F/U Visit/ Call[b] D 1095
Informed Consent[c]	X																
Inclusion/Exclusion Criteria	X	X															
CASPAR	X																
Medical/Surgical History[d]	X	X															
Vital Signs[e]/Weight/Height[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol/Nicotine Use	X																
Prior/concomitant therapy[g]	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	X	X	X	X
Physical Exam[h]	X	X							X					X	X[h]	X	
12-Lead ECG	X[i]													X	X[i] Yearly, only if required by local regulations		
Chest X-Ray[j,k]	X[j]													X[k]	X[k]	X[k]	

Activity	SCR D –35 to D –1	BL D 1	Wk 2 D 15	Wk 4 D 29	Wk 8 D 57	Wk 12 D 85	Wk 16 D 113	Wk 20 D 141	Wk 24 D 169	Wk 28 D 197	Wk 32 D 225	Wk 36 D 253	Wk 44 D 309	Wk 56 D 393	Wk 68[a] to Wk 140 (Every 12 Wks) D 477 to D 981	Wk 152 or PD D 1065	30 Day F/U Visit/ Call[b] D 1095
Bilateral X-rays of hands and feet[l]	X																
Serum Pregnancy Test at central lab[m]	X																
Local Urine Pregnancy Test[n,o]		X	X	X	X	X	X	X	X	X	X	X[o]	X[o]	X[o]	X[o]	X	X
Latent TB risk factor questionnaire[p]	X													X	X[p]	X	
Central lab QuantiFeron TB Gold test (and local PPD skin test if required)[q]	X													X	X[q]	X[q]	
Central lab tests[r] hs-CRP[s] Clinical Chemistry[t] Hematology (CBC)[t] Urinalysis[u] FSH[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[gg]

Activity	SCR D –35 to D –1	BL D 1	Wk 2 D 15	Wk 4 D 29	Wk 8 D 57	Wk 12 D 85	Wk 16 D 113	Wk 20 D 141	Wk 24 D 169	Wk 28 D 197	Wk 32 D 225	Wk 36 D 253	Wk 44 D 309	Wk 56 D 393	Wk 68[a] to Wk 140 (Every 12 Wks) D 477 to D 981	Wk 152 or PD D 1065	30 Day F/U Visit/ Call[b] D 1095
Central lab tests[r] Total cholesterol HDL-C LDL-C Triglycerides Advanced lipid testing[s]		X		X		X			X								
ESR (local lab)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Central Lab tests HIV Screening[v] Hepatitis B[w] and C Screening Rheumatoid factor Anti-CCP antibodies	X																
Blood samples for upadacitinib PK assay[x,y]			X[x]	X[x]	X[y]	X[y]	X[y]	X[y]	X[y]		X[y]			X[y]		X[y]	
Subject questionnaires[ee] HAQ-DI Patient-Pain PtGA-disease activity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Activity	SCR D –35 to D –1	BL D 1	Wk 2 D 15	Wk 4 D 29	Wk 8 D 57	Wk 12 D 85	Wk 16 D 113	Wk 20 D 141	Wk 24 D 169	Wk 28 D 197	Wk 32 D 225	Wk 36 D 253	Wk 44 D 309	Wk 56 D 393	Wk 68[a] to Wk 140 (Every 12 Wks) D 477 to D 981	Wk 152 or PD D 1065	30 Day F/U Visit/ Call[b] D 1095
Subject questionnaires[ee] SF-36 EQ-5D-5L FACIT-F WPAI BASDAI		X				X			X			X		X	X	X	
Subject Questionnaire[z,ee] SAPS		X					X		X			X		X	X[z]	X	
Tender and Swollen Joint counts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PGA-disease activity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HRU		X				X			X			X		X	X	X	
BSA Psoriasis[z]		X				X	X		X			X		X	X[z]	X	
PASI[z]		X				X	X		X			X		X	X[z]	X	
sIGA[z]		X				X	X		X			X		X	X[z]	X	
Leeds Dactylitis Index (LDI)		X				X	X		X			X		X	X	X	
Leeds/SPARCC Enthesitis Indicies (LEI)		X				X	X		X			X		X	X	X	
Psoriatic Spondylitis Assessment		X															

Activity	SCR D –35 to D –1	BL D 1	Wk 2 D 15	Wk 4 D 29	Wk 8 D 57	Wk 12 D 85	Wk 16 D 113	Wk 20 D 141	Wk 24 D 169	Wk 28 D 197	Wk 32 D 225	Wk 36 D 253	Wk 44 D 309	Wk 56 D 393	Wk 68[a] to Wk 140 (Every 12 Wks) D 477 to D 981	Wk 152 or PD D 1065	30 Day F/U Visit/ Call[b] D 1095
Adverse Event Assessment	X[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X															
Dispense Study Drug and Subject Diary[bb]		X		X	X	X	X	X	X[bb]	X	X	X	X	X	X		
Calculation of TJC/SJC responses[cc,dd]						X[cc]	X[cc]				X[dd]	X[dd]	X[dd]	X[dd]	X[dd]		
Subject Diary Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

a. These visits every 12 weeks are at: Wk 68, Wk 80, Wk 92, Wk 104, Wk 116, Wk 128, and Wk 140.

b. This on-site visit is 30 days after the last dose of study drug. For those subjects who prematurely discontinue from the study (withdrawal of informed consent) a 30-day follow-up phone call visit (and not an on-site visit) may be allowed for subjects who have completed the PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 30 day follow-up visit is not required for subjects who discontinued study drug and continued study participation with completion of at least one study visit approximately 30 days after last dose of study drug.

c. Obtain informed consent prior to performing any study related procedures.

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

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

f. Height will be measured at Screening visit only (with shoes off).

g. For concomitant medications, at Week 36 (after Week 36 assessments have been performed), per Investigator judgment, may add non-biologic DMARDs (concomitant use of up to 2 non-biologic DMARDs, except the combination of MTX and leflunomide), or increase DMARD dose.

h. For Period 1 (up to and including Week 56 visit), a full physical exam is required at the visits indicated. A symptom-directed physical exam may be performed when necessary. For Period 2 (after Week 56), a full physical exam is required approximately every 24 weeks (Wk 80, Wk 104, and Wk 128) and at the Wk 152 visit. A symptom-directed physical exam may be performed when necessary.

i. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required; provided all protocol-required documentation is available, and nothing has changed in the subject's health status since the time of the test that warrants a repeat test. If required by country regulatory authorities, an annual ECG will be performed.

j. The screening chest x-ray will not be required if a subject had a previously normal chest-x-ray (posterior-anterior and lateral views) within 90 days of Screening, provided that all protocol-required documentation is available at the site and nothing has changed in the subject's health status since the time of the test that warrants a repeat test (refer to Section 5.3.1.1 for specific requirements).

k. Obtain a chest x-ray annually for subjects with one or more TB risk factors as identified by the TB risk assessment form, subjects living in areas endemic for TB, and subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline. In the case a subject prematurely discontinues from the study drug a chest x ray should not be performed if it has been less than 48 weeks since the last examination.

l. There is no need to have a full set of x-rays of both hands and both feet as a single image could fulfill this criterion. If no prior x-rays (images and/or report) are available, subjects are required to have x-rays of both hands and feet at screening in order to document all items of the CASPAR criteria. If prior x-rays are available, but do not demonstrate radiographic evidence of juxta-articular new bone formation, subjects may have repeat x-rays of both hands and feet at screening if at least 12 weeks has passed since the prior exam.

m. For all women of childbearing potential, collect serum for pregnancy test at Screening and if any urine pregnancy test is positive at any time during the study. If the serum pregnancy test is positive the subject is considered a screen failure. If serum pregnancy test comes back borderline, a repeat test is necessary (pregnancy is an exclusion criterion). If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.

n. For all female subjects of childbearing potential, collect urine for pregnancy test at Baseline and all subsequent visits. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from study drug treatment. Refer to Section 5.3.1.1 Study Procedures Pregnancy Test for additional details.

o. If time between visits is longer than 1 month, then collect the results of the monthly at home urine pregnancy test between scheduled visits. If a urine pregnancy test is positive, the subject must stop dosing, come into the clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory. A pregnant or breastfeeding female will not be eligible for participation or continuation in this study. The monthly at home tests between scheduled on-site visits are to occur at Weeks 40, 48, 52, 60, 64, 72, 76, 84, 88, 96, 100, 108, 112, 120, 124, 132, 136, 144 and 148.

p. Latent TB risk factor questionnaire will be obtained at Screening and annually thereafter through study participation. Refer to Section 5.3.1.1 for specific requirements for TB testing and TB Prophylaxis.

q. TB testing will be performed at Screening and annually thereafter through study participation. In the case a subject prematurely discontinues from the study drug TB testing should not be performed if it has been less than 48 weeks since the last test was obtained. Refer to Section 5.3.1.1 for specific requirements for TB testing and TB Prophylaxis.

r. 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.

s. Starting from Baseline (Day 1) the hs-CRP results will not be reported to the Sponsor, Investigator, study site personnel, or the subject. For safety evaluations of signs and symptoms of infection and management of adverse events, the investigator may locally test procalcitonin. Results of tests such as hs-CRP, 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. Any local hs-CRP, CRP, or serial procalcitonin tests reported to the investigator until a subject is known to receive upadacitinib or until treatment allocation is unblinded will be recorded as protocol deviations. Samples for advanced lipid testing may be stored for batch testing and may include Apo A1, Apo B, and/or other lipid particle tests.

t. If required by country regulatory authorities, subjects who initiate or increase dose of MTX during the study should undergo ALT, AST, creatinine and CBC testing every 4 weeks for a 12 week period.

u. A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

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

w. For Japan or where mandated by local requirements: subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed approximately every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–. If necessary, HBV DNA PCR may be tested at unscheduled visits.

x. At Week 2 and Week 4 visits, PK samples should be collected prior to dosing and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample should be collected at any time during the visit.

y. PK samples should be collected at any time during the visit. Subject should follow the regular dosing schedule. Collect PK samples at Week 8, Week 12, Week 16, Week 20, Week 24, Week 32, Week 56, and at PD visit only for subjects who prematurely discontinue from study drug treatment prior to Week 56. No PK sample collection is required at Week 152.

z. PASI, BSA-Ps, sIGA, and SAPS are to be done at Week 80, Week 104, and Week 128 (every 24 weeks after Week 56).

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

bb. At Week 24, all placebo subjects will be randomized to blinded upadacitinib regardless of clinical response.

cc. At Week 16, subjects who do not achieve ≥ 20% improvement in either or both TJC and SJC compared to baseline at both Weeks 12 and 16 will be offered rescue therapy (see Section 5.2.3.4).

dd. Starting at Week 36, subjects who failed to show at least 20% improvement in either or both TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

ee. Prior to other procedures.

ff. FSH should be tested at Screening if the female subject is < 55 years of age AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined in Section 5.2.4).

gg. Only blood chemistry and hematology.

Note: Visit window is ± 3 days for the first 36 weeks and ± 7 days for the remainder of the study. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

Appendix D. Study Activities – Optional Samples for Exploratory Research or Validation Studies

Activity	SCR D –35 to D –1	BL D 1		Wk 2 D 15	Wk 4 D 29	Wk 8 D 57	Wk 12 D 85	Wk 16 D 113	Wk 20 D 141	Wk 24 D 169	Wk 28 D 197	Wk 32 D 225	Wk 36 D 253	Wk 44 D 309	Wk 56 D 393	Wk 68 to Wk 140 (Every 12 Wks) D 477 to D 981	Wk 152 or PD D 1065
Pharmacogenetic sample[a,b]		X															
Epigenetic sample[a,b,c]		X		X			X										
Transcriptomic and epigenetic sample[a,b,c]		X		X			X										
Proteomic and targeted protein investigations sample (serum)[a,b,c,d]		X		X			X										
Proteomic and targeted protein investigations sample (plasma)[a,b,c,d]		X		X			X										
Proteomic and targeted proteininvestigatioins sample (urine)[a,b,c,d]		X		X			X										

a. 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.

b. Optional with signed ICF: if the ICF is not signed, samples for exploratory research or validation studies will not be collected.

c. Subjects are preferred to have been fasting approximately 8 hours prior to collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection.

d. An effort should be made to collect prior to dosing.

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:
   - Africa
   - Eastern Europe
   - Asia
   - Russia
   - Latin America
   - Caribbean Islands
3. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
   - Chronic Cough
   - Production of Sputum
   - Blood-Streaked Sputum
   - Unexplained Weight Loss
   - Fever
   - Fatigue/Tiredness
   - Night Sweats
   - Shortness of Breath

From: http://www mayoclinic.org/diseases-conditions/tuberculosis/home/ovc-20188556
http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix F. The CASPAR Criteria

To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria,* a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis (one of a, b, c).
    a. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
    b. A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
    c. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to a patient report.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

* The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Appendix G. Local Requirements

Canada

Section 5.2.1, Inclusion Criteria

11. If female of childbearing potential, must be practicing at least two reliable methods of contraception (one highly effective method combined with one effective method or two highly effective methods, refer to Section 5.2.4), that are effective from Study Day 1 through at least 30 days after the last dose of oral study drug.

Section 5.2.4, Contraception Recommendations

Contraception Recommendation for Females

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

Postmenopausal is defined as:

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

If the female subject is < 55 years of age:

- AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.
- If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol-specified contraception is required.
- If the FSH is tested and the result is consistent with post-menopausal status, contraception is not required.

- If the FSH is tested and the result is consistent with pre-menopausal status, contraception is required, and a serum pregnancy test must be performed (see Section 5.3.1.1 pregnancy test).

For a female subject at any age:

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

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice two forms of contraception. This includes one form of highly effective contraception and one effective method of contraception or two highly effective methods. That is effective from Study Day 1 (or earlier) through at least 30 days after the last dose of oral study drug.

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

condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Male and female condoms should not be used together as they can tear or become damaged.

South Korea

Section 5.2.4, Contraception Recommendations.

Contraception Recommendation for Females

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

Postmenopausal is defined as:

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

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

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

- Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).

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

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapies. Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.