This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original and final statistical analysis plan.

1.0 Title Page

Clinical Study Protocol M15-554

A Phase 3, Randomized, Double-Blind, Study Comparing 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*

AbbVie Investigational Product:	ABT-494
Date:	10 February 2017
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:	AbbVie Inc.* Dept. R477, Bldg. AP31-3 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Contact:	PPD

* 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 Synopsis

AbbVie Inc.	**Protocol Number:** M15-554
Name of Study Drug: ABT-494	**Phase of Development:** 3
Name of Active Ingredient: ABT-494	**Date of Protocol Synopsis:** 10 February 2017
Protocol Title: A Phase 3, Randomized, Double-Blind, Study Comparing 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 ABT-494 15 mg once daily (QD) and 30 mg QD versus placebo for the treatment of signs and symptoms of 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled. The study duration will include a 35-day screening period; a 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 ABT-494 (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 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: ABT-494 15 mg QD (N = 210)

Group 2: ABT-494 30 mg QD (N = 210)

Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)

Group 4: Placebo followed by ABT-494 30 mg QD (N = 105)

Subjects will receive oral study drug QD (ABT-494 15 mg, ABT-494 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 ABT-494 15 mg QD or ABT-494 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 ABT-494 15 mg QD or ABT-494 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. 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 Section 5.2.3.2 for additional details related to prior and concomitant DMARD therapy. 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 a 20% improvement in tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) will have the option to add or modify background therapy for PsA.

At Week 24, all subjects allocated to placebo at Baseline will be switched to blinded ABT-494 (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 TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

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 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:	ABT-494
Doses:	15 mg, or 30 mg once daily
Mode of Administration:	Oral
Reference Therapy:	Matching placebo for 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 ABT-494 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. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24
6. Change from baseline in FACIT-Fatigue Questionnaire at Week 12; and Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16.

Additional key secondary efficacy endpoints (each dose of ABT-494 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;
- Change from baseline in Modified Psoriatic Arthritis Response Criteria (PsARC);
- 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;
- Change from baseline in Health Resource Utilization (HRU) Questionnaire;
- 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).

Pharmacokinetic:

Blood samples for assay of ABT-494 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.

Criteria for Evaluation (Continued):

Safety:

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

Statistical Methods:

Efficacy:

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

Period 1 Efficacy

Analysis of the Primary and Key Secondary Endpoints:

For the global analysis, comparisons of the primary and key secondary efficacy endpoints will be made between the ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

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 analysis: 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.

* Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016;68(5):1060-71.

1.2 List of Abbreviations and Definition of Terms

Abbreviations

ACR	American College of Rheumatology
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
CRF	Case Report Form
CS	Clinically Significant
csDMARD	Conventionally synthetic Disease Modifying Anti-Rheumatic Drug
CSR	Clinical Study Report
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

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

2.0 Table of Contents

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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]

ABT-494 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, ABT-494 has demonstrated inhibition of JAK1 at efficacious drug exposure levels that spare an inhibitory effect on JAK2. The enhanced selectivity of ABT-494 may have the potential for an improved benefit/risk profile by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis.

ABT-494 Clinical Development

To date, single and multiple doses of ABT-494 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, ABT-494 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 ABT-494. Results from the Phase 2 randomized controlled studies in subjects with RA are available. Efficacy of treatment with ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 (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 ABT-494 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 ABT-494 compared with placebo (50%). At all doses of ABT-494 compared to placebo, significantly higher proportions of subjects achieved LDA and clinical remission at Week 12.

Safety results across the studies showed that ABT-494 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 ABT-494 (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 ABT-494 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 ABT-494.

Phase 3 Studies with ABT-494

Six multi-country randomized controlled trials (RCTs) inclusive of approximately 4,425 subjects are planned or ongoing for ABT-494 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 ABT-494 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 ABT-494 as monotherapy. A total of 3 dose regimens of ABT-494 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 ABT-494 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. ABT-494 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 ABT-494 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 ABT-494 in Phase 3 in subjects with PsA.

4.0 Study Objective

Period 1

1. To compare the efficacy of ABT-494 15 mg once daily (QD) and 30 mg QD versus placebo for the treatment of signs and symptoms of 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 15 mg QD, and 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. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening may not be enrolled.

The study duration will include a 35-day screening period; a 56-week blinded period which includes 24 weeks of double-blind, placebo-controlled treatment followed by 32 weeks of treatment blinded to dose of ABT-494 (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 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: ABT-494 15 mg QD (N = 210)

Group 2: ABT-494 30 mg QD (N = 210)

Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)

Group 4: Placebo followed by ABT-494 30 mg QD (N = 105)

Subjects will receive oral study drug QD (ABT-494 15 mg, ABT-494 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 ABT-494 15 mg QD or ABT-494 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 ABT-494 15 mg QD or ABT-494 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. 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 a 20% improvement in tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) as follows: 1) add or modify doses of NSAIDs, acetaminophen/paracetamol, and/or low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or 2) receive 1 intra-articular or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis as described in Section 5.2.3.4 (Rescue Therapy). Change in dose or addition of a non-biologic DMARDs is not permitted at Week 16.

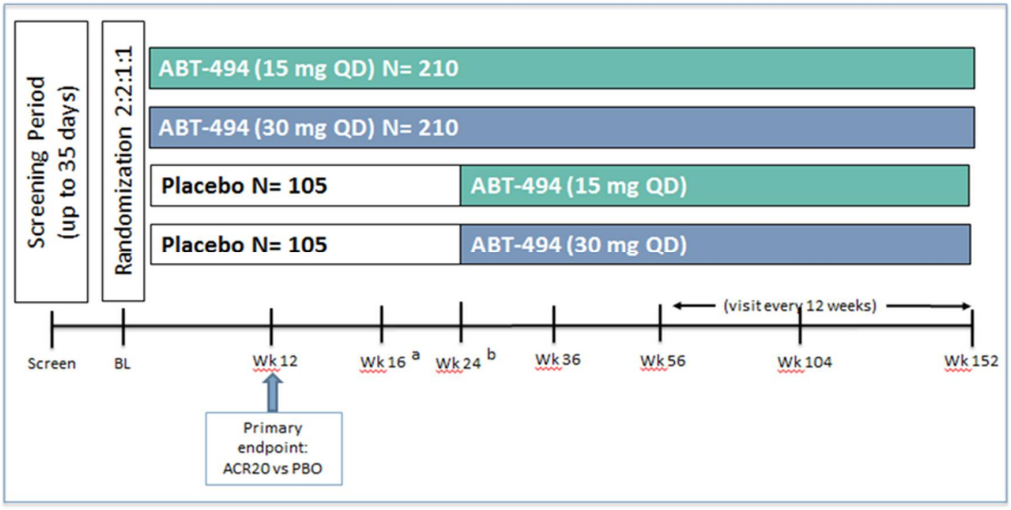
At Week 24, all subjects allocated to placebo at Baseline will be switched to blinded ABT-494 (randomized at baseline to either 15 mg QD or 30 mg QD) treatment regardless of clinical response.

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 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 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 a 20% improvement in 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 ABT-494 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Appendix C. Lab values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure with no additional re-screening possible. Redrawing samples if initial samples were unable to be analyzed would not count as a retest since initial result was never obtained.

Subjects that initially screen-fail for the study are permitted to re-screen once following re-consent 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 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.

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 TJC and SJC compared to baseline at 2 consecutive visits (see Section 5.2.3.1) will be discontinued from study drug treatment. Subjects may discontinue study drug treatment, but may choose to continue to participate in the study (refer to Section 5.4.1 for additional details). Subjects who prematurely discontinue study drug should complete a Premature Discontinuation visit (PD visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix C and adhere to all study procedures except for dispensing study drug, 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), procedures for the Premature Discontinuation of Study should be completed as outlined below.

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

Follow-Up Period

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.

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. 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.

7. 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.

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

9. 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.

10. 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 H for local requirements.

If male and subject is sexually active with a female partner(s) of childbearing potential, he must practice the protocol specified contraception from the Baseline visit through at least 30 days after last dose of study drug (Section 5.2.4).

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

11. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. 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 – 8	To select the appropriate subject population
9, 10	The effect of ABT-494 on pregnancy and reproduction is unknown
11	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 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 (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 only);
        - 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:
    - Clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 500 msec.
    - History of any of the following cardiovascular conditions:
        - Moderate to severe congestive heart failure (New York Heart Association class III or IV);

- Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
- Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
- Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.

- Subject has been a previous recipient of an organ transplant;
- 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 NMSC or localized carcinoma in situ of the cervix;
- History of demyelinating disease such as Multiple Sclerosis or neurologic symptoms suggestive of demyelinating disease (including myelitis);
- 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 prohibited concomitant psoriasis treatments within the specified timeframe prior to Baseline:

- Oral retinoids ≥ 4 weeks;
- Psoralens and Ultraviolet A (PUVA) ≥ 4 weeks;
- Ultraviolet A (UVA) or Ultraviolet B (UVB) ≥ 2 weeks;
- Topical treatments (except low potency (Class VI or Class VII) topical corticosteroids on the palms, soles, face, inframammary area, and groin only) ≥ 2 weeks, with the exception of the following:
  - Shampoos that contain no corticosteroid

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

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. 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.
10. 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 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.
11. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.
12. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
13. Male subject who is considering fathering a child or donating sperm during the study or for approximately 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 ABT-494.

The Rationale for the Exclusion Criteria

1 – 3	To select the appropriate subject population
12, 13	The impact of ABT-494 on pregnancies is unknown
4 – 11, 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 PsA/PsO Therapy

In Period 1, if subjects are on background DMARDs they must 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 must 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 must 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 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 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 NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or receive 1 intra-articular or intra-tendon sheath corticosteroid injection for 1 peripheral joint 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:

- Shampoos that contain no corticosteroid
- Bland (without beta or alpha hydroxy acids) emollients
- Low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only.

In Periods 1 and 2, starting at Week 16 (after Week 16 assessments have been performed) and thereafter, subjects may use any topical therapy for PsO per investigator judgment.

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

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

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

Intra-articular, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids are NOT allowed in Period 1 up to Week 36 unless a subject qualifies for rescue therapy at the Week 16 visit (Section 5.2.3.4).

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
Indinavir	St. John's Wort
Itraconazole	
Ketoconazole	
Lopinavir/Ritonavir	
Mibefradil	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Troleandomycin	
Voriconazole	

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.

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.

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 a 20% improvement in tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16) will have the option to add or modify doses of NSAIDs, acetaminophen/paracetamol, and/or low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), and/or receive 1 intra-articular or intra-tendon sheath corticosteroid injection for 1 peripheral joint or 1 enthesis. Doses of non-biologic DMARDs may not exceed maximums defined in inclusion criteria (Section 5.2.1). Change in dose or addition of a non-biologic DMARD is not permitted at Week 16.

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 (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 a follicle-stimulating hormone (FSH) level > 40 IU/L.

If the female subject is < 55 years of age:

- AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.
- If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol-specified contraception is required.
- If the FSH is tested and the result is consistent with post-menopausal status, contraception is not required.
- If the FSH is tested and the result is consistent with pre-menopausal status, contraception is required, and a serum pregnancy test must be performed (see Section 5.3.1.1 pregnancy test).

For a female subject at any age:

- Female subjects with menses within the past 12 months are of childbearing potential and FSH is therefore not required but contraception is required.

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

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

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 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 has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence) e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable.

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

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational

therapies. 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 H for local requirements.

Contraception Recommendation for Males

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

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

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

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

Additionally, male subjects must agree not to donate sperm from the Baseline Visit through 30 days after the last dose of study drug.

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

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational

therapies. 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 H for local requirements.

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. 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 subjects 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.

Physical Exam

A complete physical examination will be performed at the designated study visits as specified in Appendix C. The physical examination at the Screening 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.

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. ECG with QT interval corrected for heart rate using Friedericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed. In these cases, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible site monitor and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided 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 other findings that are clinically significant, the Investigator must contact the AbbVie TA MD before enrolling the subject.

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

X-Rays of the Hands and Feet

If Item 5 of the CASPAR (Appendix G) 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 juxtaarticular 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 juxtaarticular 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 TB risk factors as identified by the TB risk assessment form (Appendix F) for subjects living in areas endemic for TB or

for subjects with newly positive PPD and/or QuantiFERON-TB Gold test 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 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.

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

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

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

At screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix F) and tested for TB infection by QuantiFERON-TB Gold test. The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines). The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF.

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

For subjects with a negative TB test result at Screening or most recent evaluation, an annual TB re-test will be performed. The TB test(s) to be performed depends on local guidelines and whether or not the site has capacity to perform QuantiFERON-TB Gold testing (see below). If an annual TB test is newly positive (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Expert consultation can be considered per Investigator's discretion.

TB test:

- For regions that require both PPD and QuantiFERON-TB Gold testing, both will be performed. A positive TB test is defined by local guidelines (for example, in some countries, both PPD and QuantiFERON-TB Gold are performed, and if either one is positive, the TB test is considered positive).

- In the absence of local guidelines defining a positive result when both PPD and QuantiFERON-TB Gold tests are performed, then the QuantiFERON-TB Gold test result will be the TB test result (QuantiFERON-TB Gold supersedes PPD).
- If a site has the capacity to perform both PPD and QuantiFERON-TB Gold tests, and local guidelines require only one test to be performed, then the QuantiFERON-TB Gold 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 for RA subjects is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and the TB Skin Test should be considered positive.

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

If the QuantiFERON-TB Gold test is indeterminate, the site should repeat the test with another blood sample and/or perform a PPD test. If the second QuantiFERON-TB Gold test is also indeterminate, then the subject is considered to be positive.

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with no signs or symptoms and a

CXR not suggestive of active TB may be enrolled after initiation of TB prophylaxis (see below). Subjects with evidence of active TB must not be enrolled.

TB prophylaxis:

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

Of note: Rifampicin is not allowed for TB prophylaxis.

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

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

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

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

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

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

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.

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

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.

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.

f. At Screening only. For Japan only: for subjects with HBs Ab+ and/or HBc Ab+ at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from study drug treatment. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and HBs Ab+.

Table 2. Clinical Laboratory Tests (Continued)

g. All subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Appendix F) and tested for TB infection by QuantiFERON-TB Gold test 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. The hs-CRP results starting from Baseline (Day 1) 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, serum amyloid A and procalcitonin may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. Any hs-CRP, CRP, serial serum amyloid A, or serial procalcitonin local tests reported to the investigator 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.

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

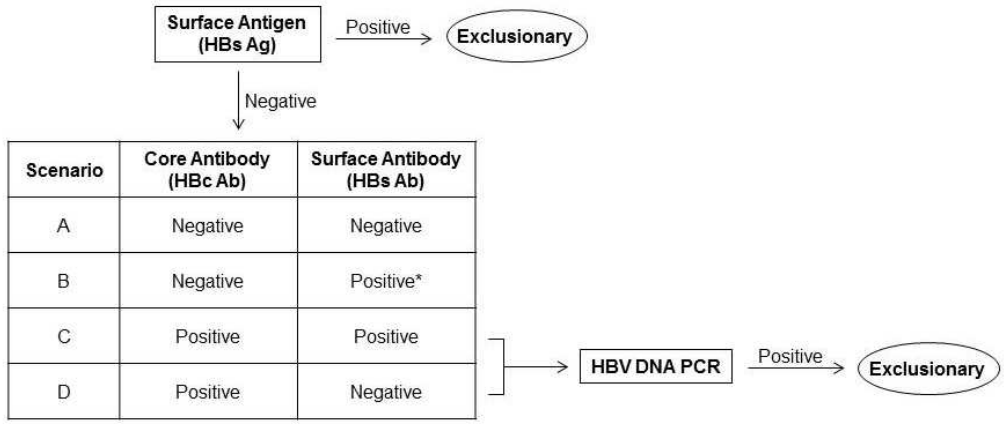
A positive result for HBs Ag will be exclusionary.

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 and the subject may be enrolled (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 exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.
  - For Japan only: for subjects with HBs Ab+ and/or HBc Ab+ at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. In cases where the recurrence of HBV-DNA is observed, the

subject should be discontinued from study drug treatment. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and HBs Ab+.

Figure 2. Criteria for HBV DNA PCR Qualitative Testing



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

Hepatitis C:

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: ABT-494 15 mg QD (N = 210)
- Group 2: ABT-494 30 mg QD (N = 210)
- Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)
- Group 4: Placebo followed by ABT-494 30 mg QD (N = 105)

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 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.

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.

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.

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. If possible, the investigator assessments should be performed by an independent and blinded assessor who should not perform any other study related procedures. In order to minimize variability, the same independent assessor should evaluate the subject at each visit for the duration of the trial. A back-up independent assessor should be identified. The independent assessor must be a qualified medical professional (e.g., nurse, physician's assistant, or physician). 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 independent 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.

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 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.

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 by the physician is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved.

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.

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.

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.

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.

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.

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.

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.

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 ABT-494 (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 ABT-494 PK Assay (Period 1 Only)

Blood samples (plasma) for assay of ABT-494 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 ABT-494 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

<u>The key multiplicity adjusted secondary efficacy endpoints (each dose of ABT-494 versus placebo) are:</u>

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. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
6. Change from baseline in FACIT-Fatigue Questionnaire at Week 12; and change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) Questionnaire at Week 16.

Additional key secondary efficacy endpoints (each dose of ABT-494 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 Secondary Variables

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;
- 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;
- Change from baseline in Modified Psoriatic Arthritis Response Criteria (PsARC);
- 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;
- Change from baseline in Health Resource Utilization (HRU) Questionnaire;
- 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 ABT-494 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 ABT-494

oral clearance (CL/F) and volume of distribution (V/F). Additional parameters for ABT-494 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 ABT-494 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 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
- Subject develops a gastrointestinal perforation
- 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 TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment

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, 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: ABT-494.

ABT-494 (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.

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
ABT-494	Oral	Tablet	15 mg 30 mg	AbbVie
ABT-494 Matching Placebo	Oral	Tablet	NA	AbbVie

5.5.2.1 Packaging and Labeling

ABT-494 and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the kits. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug(s)

ABT-494 must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects 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: ABT-494 15 mg QD (N = 210)
- Group 2: ABT-494 30 mg QD (N = 210)
- Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)
- Group 4: Placebo followed by ABT-494 30 mg QD (N = 105)

Subjects will receive oral study drug QD (ABT-494 15 mg, ABT-494 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 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 5.3.2.1 regarding Week 2 and Week 4 visits).

Each subject's dosing schedule should be closely monitored by the site at each study visit by careful review of the subject's 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).

ABT-494/Placebo (daily dosing):

- If a subject should forget to take their ABT-494 (or matching placebo) dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.
- If the subject experiences a study drug interruption > 14 consecutive days during the first 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. If study drug treatment is interrupted or withdrawn in Periods 1 or 2, study drug administration must be stopped.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personnel with direct oversight of the conduct and management of the 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 ABT-494/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 that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document and by registering the arrival of drug through the IRT. The original Proof of Receipt Note and the IRT confirmation sheet will be kept in the site files as a record of what was received.

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

All empty/used study drug packaging will be inventoried by the site and verified by the site monitor. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary. Empty/used packaging will be retained (unless prohibited by local law) until the site monitor is on site to confirm the returned study drug. Site monitor(s) and site staff will complete study drug accountability via IRT, source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible. After drug accountability has been completed, used packaging and unused study drug will be destroyed on site according to local procedures or regulations or returned to the destruction depot by the site monitor (for those sites that do not meet AbbVie's documentation requirements for

on-site destruction). The use of a third party vendor for drug destruction must be pre-approved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This study includes two periods.

Period 1 is 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 ABT-494 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 ABT-494 versus placebo for achieving the primary endpoint (ACR20 at Week 12) and other secondary efficacy parameters at Weeks 12 – 24. At Week 24 all subjects will be given ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 have been selected for this study in order to perform limited dose ranging in subjects with PsA. The ABT-494 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 ABT-494 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 ABT-494 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, ABT-494 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 ABT-494 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, herpes zoster, and TB;
- Gastrointestinal perforations;
- Cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Malignancy and lymphoproliferative disorders;
- Lipid effects;
- Anemia and decreased hemoglobin;
- Decreased neutrophil counts;

- Decreased lymphocyte counts;
- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Elevated creatine phosphokinase (CPK).

6.1.2 Adverse Event Severity

The investigator will classify AEs according to the Rheumatology Common Toxicity Criteria v2.0. (Appendix E).

6.1.3 Relationship to Study Drug

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

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

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

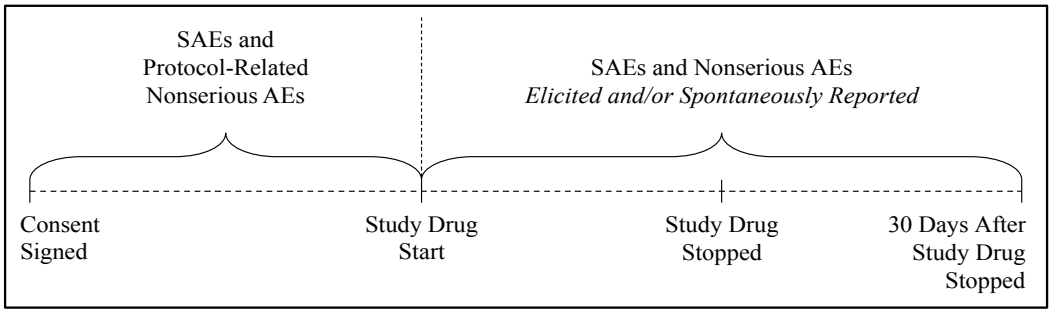
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until 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;

- Cardiovascular procedures (SAE Supplemental Procedure eCRF).

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

- Hepatic;
- Renal;
- Herpes Zoster Infection.

In the case of creatine phosphokinase increased > 4 × ULN, a supplemental CPK 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:	PPD [redacted]
FAX to	[redacted]

For safety concerns, contact the Immunology Safety Team at:

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

Phone: PPD [redacted]
Email: [redacted]

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

Therapeutic Area Medical Director (TA MD):

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:	PPD

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 and the USA will be the most current version of the Investigator's Brochure for ABT-494.

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

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued 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 and female partners of male subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. Male subjects should refrain from donating sperm for up to 30 days post last dose of study drug. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

6.1.7 Toxicity Management

The toxicity management of the AEs including 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. If study drug has been interrupted for a serious infection for more than 7 consecutive days during the first 24 weeks of the study or 30 consecutive days thereafter, the subject must be discontinued from study drug. Subjects who develop active TB must be discontinued from study drug.

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

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant 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.

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, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1000 µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its baseline value. • Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
Absolute lymphocyte counts (ALC)	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its baseline value.
Total white blood cell count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its baseline value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

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

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Discontinue study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5. o INR will only be measured in subjects with ALT or AST > 3 × ULN by the central lab by reflex testing and confirmation is not needed for consideration in toxicity management criteria. • Discontinue study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • Discontinue study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. • Discontinue study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. For all of the above ALT or AST elevation scenarios, complete supplemental hepatic eCRF.
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × baseline value. • If confirmed serum creatinine ≥ 2mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
Creatine Phosphokinase	• If any confirmed CPK value ≥ 4 × ULN (if symptomatic or asymptomatic), complete supplemental CPK eCRF. • If confirmed CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug, complete supplemental CPK eCRF, and contact AbbVie TA MD.

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 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: Alternate Contact:

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

Examples of protocol deviations include the following:

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

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).

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 ABT-494 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, weight, 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 ABT-494 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 ABT-494 dose group and the combined placebo groups will be carried out using the analysis of covariance model with treatment group as the fixed factor, and the corresponding baseline value and the main stratification factors as the covariates.

8.1.4.3 Additional Secondary Efficacy Variables

Additional secondary 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. The group of 2 endpoints at the end of the ranking sequence will be tested using the Hochberg procedure, conditional on significance of higher ranked endpoints. 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.

Pattern Mixture Model (PMM): The PMM approach classifies the subjects into several distinct dropout patterns; the overall treatment effect is estimated by combining the results from all patterns.

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. PMM will be used as a sensitivity analysis for key continuous endpoints.

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

Missing safety data will not be imputed.

8.1.5.2 Analysis of Adverse Events

Unless otherwise specified, the following conventions apply for both 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 (including but not limited to serious infections, opportunistic infection, herpes zoster, TB, gastrointestinal perforations, malignancies and lymphoproliferative disorders, cardiovascular events [including MACE], renal dysfunction, anemia, increased CPK, and drug-related hepatic disorders) will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the 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, Vital Sign, and ECG Data

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

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

The laboratory data will be categorized as Grade 1, Grade 2, Grade 3, and Grade 4 according to OMERACT criteria (Rheumatology Common Toxicity Criteria v.2.0). For creatinine phosphokinase, serum creatinine, and parameters that are not covered in the OMERACT criteria, NCI CTC criteria will be used. The shift tables will tabulate the number and percentage of subjects with baseline and post-baseline values by grade levels. Listings will be provided for potentially clinically significant laboratory values and vital signs.

8.1.6 Pharmacokinetic and Exposure-Response Analyses

Individual ABT-494 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 ABT-494 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 ABT-494 exposure and clinical observations will be explored.

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 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.

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.

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.

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.

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 CRF 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, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

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

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

The 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 ABT-494 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 ABT-494.

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 ABT-494.
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 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: 10 February 2017

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
PPD		Immunology Therapeutic Area
		Immunology Therapeutic Area
		Pharmacovigilance and Patient Safety
		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 1123
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[i]	X													X	X		
Chest X-Ray[j,k]	X[j]													X[k]	X[k]	X[k]	
Bilateral X-rays of hands and feet[l]	X																
Serum Pregnancy Test at central lab[m]	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 1123
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	
Central lab tests[r] hs-CRP[s] Clinical Chemistry[t] Hematology (CBC)[t] Urinalysis[u] FSH[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
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	

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 1123
Other Central Lab tests HIV Screening[v] Hepatitis B and C Screening Rheumatoid factor Anti-CCP antibodies	X					X[w]			X[w]								
Blood samples for ABT-494 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[z] HAQ-DI Patient-Pain PtGA-disease activity		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Subject questionnaires[z] SF-36 EQ-5D-5L FACIT-F WPAI BASDAI		X				X			X			X		X	X	X	
Subject Questionnaire[z] SAPS		X					X		X			X		X	X	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	

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 1123
HRU		X				X			X			X		X	X	X	
BSA Psoriasis[z]		X				X	X		X			X		X	X	X	
PASI[z]		X				X	X		X			X		X	X	X	
sIGA		X				X	X		X			X		X	X	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															
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	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.
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 TB risk factors as identified by the TB risk assessment form for subjects living in areas endemic for TB or for subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline.
l. 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 juxtaarticular 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 only at Screening. 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 females 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 in to 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, Wk 56, Wk 112, and Wk 152. Refer to Section 5.3.1.1 for specific requirements for TB testing and TB Prophylaxis.
For all women of childbearing potential, collect serum for pregnancy test only at Screening. 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.

q. TB testing will be performed at Screening, Wk 56, Wk 112, and Wk 152. 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. The hs-CRP results starting from Baseline (Day 1) 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, serum amyloid A and procalcitonin may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. Any hs-CRP, CRP, serial serum amyloid A, or serial procalcitonin local tests reported to the investigator 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.
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).

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 only: for subjects with HBs Ab+ and/or HBc Ab+ at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from study drug treatment. Retesting at Week 12 and Week 24 is not necessary for subjects that have a history of HBV vaccine and HBs Ab+.

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. For subjects who prematurely discontinue from study drug treatment prior to Week 56, PK sample will be collected at any time during the PD visit.

z. After Week 56, PASI, BSA-Ps, and SAPS are to be done every 24 weeks (at Wk 80, Wk 104, and Wk 128 visits) and at the Wk 152/PD visit.

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 ABT-494 regardless of clinical response.

cc. At Week 16, subjects who do not achieve ≥ 20% improvement in 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 TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

ee. Prior to other procedures.

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 365	Wk 68 to Wk 140 (Every 12 Wks) D 449 to D 1037	Wk 152 or PD D 1093
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. Rheumatology Common Toxicity Criteria v.2.0 Example

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

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

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

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

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

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

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

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

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

I. Neuropsychiatric (continued)				
I11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalization
J. Pulmonary				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitation, requiring hospitalisation
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O_2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity – DLCO)	76% – 90% of pre-treatment value	51% – 75% of pre-treatment value	26% – 50% of pre-treatment value	≤ 25% of pre-treatment value

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

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

Appendix F. Latent TB Risk Assessment Form Example

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
   - 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 G. 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 H. Local Requirements

Canada

Section 5.2.1, Inclusion Criteria

6. If female of childbearing potential, must be practicing at least two reliable methods of contraception (one highly effective method combined with one effective method, refer to Section 5.2.4), that are effective from Study Day 1 through at least 150 days after the last dose of subcutaneous study drug and through at least 30 days after the last dose of oral study drug.

   If male and subject is sexually active with a female partner(s) of childbearing potential, he must practice the protocol-specified contraception from the Baseline visit through at least 30 days after last dose of oral study drug (refer to Section 5.2.4).

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/L.

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. That is effective from Study Day 1 (or earlier) through at least 150 days after the last dose of subcutaneous study drug and through at least 30 days after the last dose of oral study drug.

- Highly effective methods:
  - Hormonal contraceptives started at least 2 months prior to randomization (e.g., combined [estrogen and progestogen containing] [oral contraceptives, patch, vaginal ring, injectables, and implants);
  - Intrauterine device (IUD) or intrauterine system (IUS);
  - Vasectomy and tubal ligation.

- Effective methods:
  - Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)
  - Note: The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception. When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Male and female condoms should not be used together as they can tear of become damaged.

Contraception Recommendation for Males

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

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

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

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

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

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/L.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control that is effective from Study Day 1 (or earlier) through at least 150 days after the last dose of subcutaneous study drug and through at least 30 days after the last dose of oral study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).

- Intrauterine hormone-releasing system (IUS).

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

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

Contraception Recommendation for Males

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

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

- Condom use and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential). Additionally, male subjects must agree not to donate sperm from Study Day 1 through 30 days after the last dose of oral study drug.

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

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational

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

Document Approval

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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 Change 1, 2 and Amendments 1, 2, 2.01 (VHP Countries), 3, 4, 5, 6 and 7

AbbVie Investigational Product:	ABT-494
Date:	01 April 2020
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 Bldg. AP31-2 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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Sponsor/Emergency Contact:	PPD

* 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

The purpose of this amendment is to:

- Apply administrative changes throughout protocol

  Rationale: *Revised text to improve consistency and readability, and/or provide clarification.*
- Update Section 3.2 Benefits and Risks, paragraph 4

  Rationale: *To update safety information regarding risk of pregnancy in female partners of male subjects.*
- Update Section 5.2.3.2 Permitted Background Therapy, paragraph 4

  Rationale: *To ensure subject safety by clarifying that oral corticosteroid dose may not exceed the maximum dose (equivalent to prednisone ≤ 10 mg/day) defined in the inclusion criteria, Section 5.2.1.*
- Update Section 5.3.1.1 Study Procedures, Hepatitis Screening, Last Bullet

  Rationale: *Where mandated that testing should be performed every 12 weeks, clarified that HBV DNA PCR may be tested at unscheduled visits.*
- Update Section 5.3.1.1 Study Procedures, Hepatitis Screening, Figure 2 footnote

Rationale: *Where mandated that testing should be performed every 12 weeks, clarified that HBV DNA PCR may be tested at unscheduled visits.*

- Update Section 5.4.1 Discontinuation of Individual Subjects

  Rationale: *To clarify that the development of gastrointestinal perforation due to appendicitis or mechanical injury will not require study drug discontinuation as these types of events differ from those of potential concern with IL-6 inhibition.*

  Rationale: *To add an additional safety precaution for subjects, given the recent concerns raised for the JAK inhibitor class regarding thrombosis risk.*

- Update Section 5.5.7 Drug Accountability

  Rationale: *Verification of study drug receipt is done in the IRT and paper documents are no longer required nor kept in site files.*

- Update Section 6.1.7 Toxicity Management

  Rationale: *To clarify that the development of gastrointestinal perforation due to appendicitis or mechanical injury will not require study drug discontinuation as these types of events differ from those of potential concern with IL-6 inhibition.*

  Rationale: *To add an additional safety precaution for subjects, given the recent concerns raised for the JAK inhibitor class regarding thrombosis risk.*

  Rationale: *To clarify when additional eCRFs are required in the management of select laboratory abnormalities.*

- Update Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values

  Rationale: *To clarify guidelines for toxicity management and maintain subject safety.*

- Update Section 6.1.9 Cardiovascular Adjudication Committee

  Rationale: *To clarify that the cardiovascular adjudication committee also assesses potential embolic and thrombotic AEs.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *To update a title in the List of Protocol Signatories.*

- Update Appendix C, Study Activities, Other Central Lab tests

Rationale: *To remove the 'X' from Week 12 and Week 24 to clarify that these timepoints are only relevant for Hepatitis B testing for Japan or where mandated by local requirements.*

- Update Appendix C, Study Activities, Footnote w

  Rationale: *Where mandated that testing should be performed every 12 weeks, clarified that HBV DNA PCR may be tested at unscheduled visits.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-554
Name of Study Drug: ABT-494	**Phase of Development:** 3
Name of Active Ingredient: ABT-494	**Date of Protocol Synopsis:** 01 April 2020
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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 (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: ABT-494 15 mg QD (N = 210)

Group 2: ABT-494 30 mg QD (N = 210)

Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)

Group 4: Placebo followed by ABT-494 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 (ABT-494 15 mg, ABT-494 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 ABT-494 15 mg QD or ABT-494 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 ABT-494 15 mg QD or ABT-494 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 ABT-494 (randomized at baseline to either 15 mg QD or 30 mg QD) treatment regardless of clinical response.

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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.

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:	ABT-494
Doses:	15 mg, or 30 mg once daily
Mode of Administration:	Oral
Reference Therapy:	Matching placebo for 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 ABT-494 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 ABT-494 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 ABT-494 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.

Criteria for Evaluation (Continued):

Safety:

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

Statistical Methods:

Efficacy:

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

Period 1 Efficacy

Analysis of the Primary and Key Secondary Endpoints:

For the global analysis, comparisons of the primary and key secondary efficacy endpoints will be made between the ABT-494 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 ABT-494 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 ABT-494 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.

Statistical Methods (Continued):

Pharmacokinetic:

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

Safety:

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

2.0 Table of Contents

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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]

ABT-494 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, ABT-494 has demonstrated inhibition of JAK1 at efficacious drug exposure levels that spare an inhibitory effect on JAK2. The enhanced selectivity of ABT-494 may have the potential for an improved benefit/risk profile by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis.

ABT-494 Clinical Development

To date, single and multiple doses of ABT-494 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, ABT-494 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 ABT-494. Results from the Phase 2 randomized controlled studies in subjects with RA are available. Efficacy of treatment with ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 (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 ABT-494 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 ABT-494 compared with placebo (50%). At all doses of ABT-494 compared to placebo, significantly higher proportions of subjects achieved LDA and clinical remission at Week 12.

Safety results across the studies showed that ABT-494 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 ABT-494 (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 ABT-494 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 ABT-494.

Phase 3 Studies with ABT-494

Six multi-country randomized controlled trials (RCTs) inclusive of approximately 4,425 subjects are planned or ongoing for ABT-494 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 ABT-494 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 ABT-494 as monotherapy. A total of 3 dose regimens of ABT-494 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 ABT-494 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. ABT-494 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 ABT-494 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 ABT-494 in Phase 3 in subjects with PsA.

The safety profile specific to ABT-494 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 ABT-494 therapy.

The results of all genetic toxicology testing indicate that ABT-494 is not genotoxic, however ABT-494 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 ABT-494 can be found in the current Investigator's Brochure.

4.0 Study Objective

Period 1

1. To compare the efficacy of ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 dose of ABT-494 (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: ABT-494 15 mg QD (N = 210)

Group 2: ABT-494 30 mg QD (N = 210)

Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)

Group 4: Placebo followed by ABT-494 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 (ABT-494 15 mg, ABT-494 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 ABT-494 15 mg QD or ABT-494 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 ABT-494 15 mg QD or ABT-494 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 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).

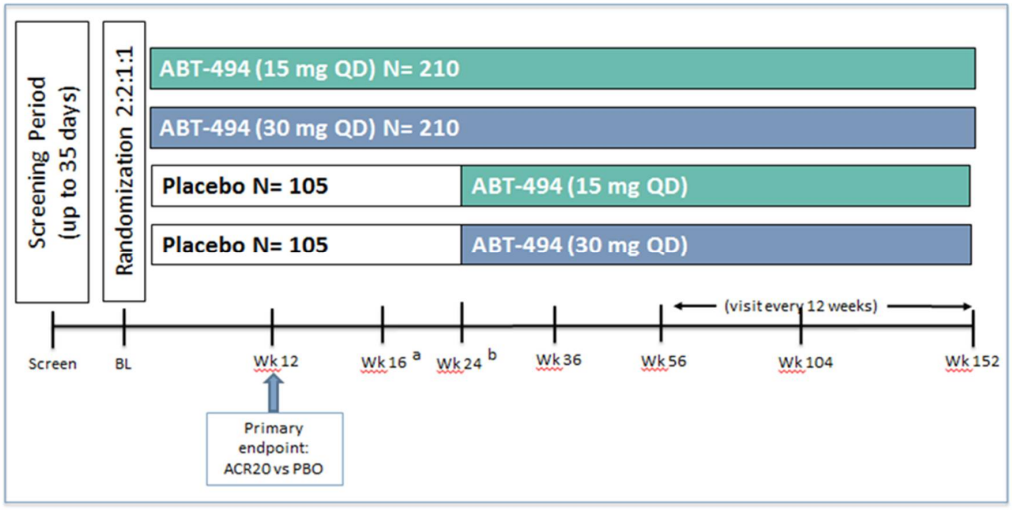
At Week 24, all subjects allocated to placebo at Baseline will be switched to blinded ABT-494 (randomized at baseline to either 15 mg QD or 30 mg QD) treatment regardless of clinical response.

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 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 ABT-494 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

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.

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. 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. 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 ABT-494 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 ABT-494.

The Rationale for the Exclusion Criteria

1 – 3, 11	To select the appropriate subject population
13	The impact of ABT-494 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.

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.

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.

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.

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. 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.

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 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)

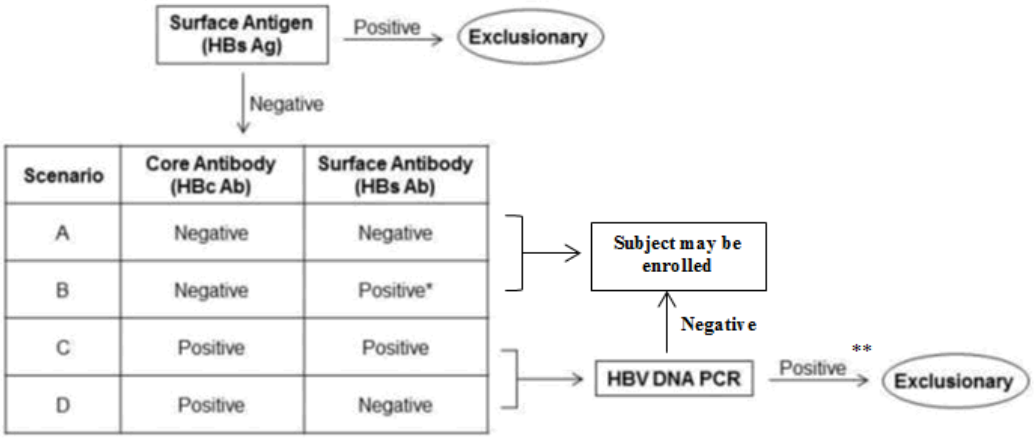
A positive result for HBs Ag will be exclusionary.

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: ABT-494 15 mg QD (N = 210)
- Group 2: ABT-494 30 mg QD (N = 210)
- Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)
- Group 4: Placebo followed by ABT-494 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.

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.

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.

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 ABT-494 (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 ABT-494 PK Assay (Period 1 Only)

Blood samples (plasma) for assay of ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 oral clearance (CL/F) and volume of distribution (V/F). Additional parameters for ABT-494 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 ABT-494 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 (other than due to 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: ABT-494.

ABT-494 (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.

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
ABT-494	Oral	Tablet	15 mg 30 mg	AbbVie
ABT-494 Matching Placebo	Oral	Tablet	NA	AbbVie

5.5.2.1 Packaging and Labeling

ABT-494 and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the kits. All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug(s)

ABT-494 must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the

context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects 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: ABT-494 15 mg QD (N = 210)
- Group 2: ABT-494 30 mg QD (N = 210)
- Group 3: Placebo followed by ABT-494 15 mg QD (N = 105)
- Group 4: Placebo followed by ABT-494 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 (ABT-494 15 mg, ABT-494 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).

ABT-494/Placebo (daily dosing):

- If a subject should forget to take their ABT-494 (or matching placebo) dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.
- If the subject experiences a study drug interruption > 14 consecutive days during the first 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 ABT-494/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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 have been selected for this study in order to perform limited dose ranging in subjects with PsA. The ABT-494 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 ABT-494 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 ABT-494 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, ABT-494 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 ABT-494 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.

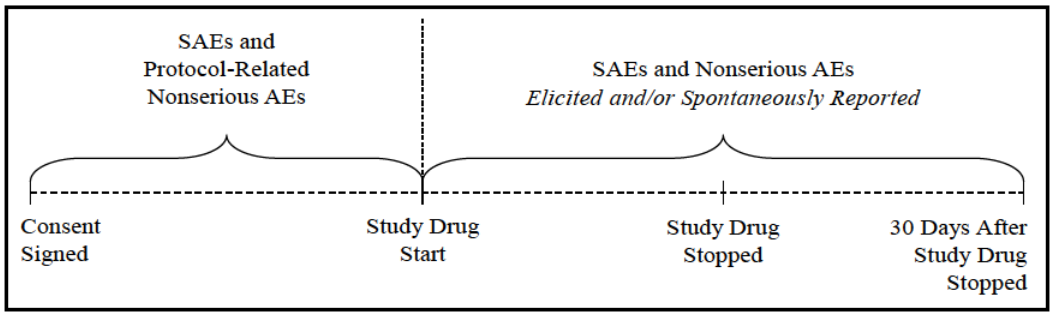
If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the serious adverse event.

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, 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:	PPD
FAX to	

For safety concerns, contact the Immunology Safety Team at:

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

Phone: PPD
Email:

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

Therapeutic Area Medical Director (TA MD):

PPD

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:	PPD [redacted]

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 ABT-494.

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. 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.

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 immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5. 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). • Interrupt study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. • 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: Alternate Contact:

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

Examples of protocol deviations include the following:

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

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).

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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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 ABT-494 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.

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.

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.

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.

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 CRF 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, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

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

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

a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The 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 ABT-494 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 ABT-494. 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 ABT-494.
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:	01 April 2020

Signature of Principal Investigator Date

Name of Principal Investigator (printed or typed)

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the 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
PPD		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]		
Chest X-Ray[j,k]	X[j]													X[k]	X[k]	X[k]	
Bilateral X-rays of hands and feet[l]	X																
Serum Pregnancy Test at central lab[m]	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
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]
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	

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
Other Central Lab tests HIV Screening[v] Hepatitis B[w] and C Screening Rheumatoid factor Anti-CCP antibodies	X																
Blood samples for ABT-494 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	
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	

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
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															
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 ABT-494 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.

Appendix H. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 3.2 Benefits and Risks
Fourth paragraph, last sentence previously read:

Based on an embryofetal development study in rats, there is judged to be no risk associated with administration of upadacitinib to male partners of females of childbearing potential.

Has been changed to read:

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.

Section 5.2.3.2 Permitted Background Therapy
Fourth paragraph, first sentence previously read:

In addition, at Week 36 (after Week 36 assessments have been performed) and thereafter, initiation of or change in 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.

Has been changed to read:

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.

Section 5.2.3.2 Permitted Background Therapy
Fourth paragraph, last sentence previously read:

Doses of non-biologic DMARDs may not exceed maximums defined above and in inclusion criteria (Section 5.2.1).

Has been changed to read:

Doses of non-biologic DMARDs and oral corticosteroids may not exceed maximums defined above and in inclusion criteria (Section 5.2.1).

Section 5.3.1.1 Study Procedures
Subsection Hepatitis Screening
Heading "Hepatitis B:"
Third paragraph, last bullet previously read:

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 every 12 weeks. Retesting every 12 weeks is not necessary for subjects that have a history of HBV vaccine and are HBs Ab+ and HBc Ab–.

Has been changed to read:

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
Figure note "" previously read:**

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 every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and is HBs Ab+ and HBc Ab–.

Has been changed to read:

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.

Section 5.4.1 Discontinuation of Individual Subjects
Eleventh bullet previously read:

Subject develops a gastrointestinal perforation

Has been changed to read:

Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injury)

Section 5.4.1 Discontinuation of Individual Subjects
Add: new last bullet

Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.

Section 5.5.7 Drug Accountability
First paragraph previously read:

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

Has been changed to read:

The Investigator or his/her representative will verify in the IRT that study drug supplies are received intact and in the correct amounts.

Section 6.1.7 Toxicity Management
Fifth paragraph, last sentence previously read:

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

Has been changed to read:

If the diagnosis of gastrointestinal perforation is confirmed (other than due to appendicitis or mechanical injury), the subject must be discontinued from study drug.

Section 6.1.7 Toxicity Management
Ninth paragraph
Add: new last sentence

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.

Section 6.1.7 Toxicity Management
Eleventh paragraph
Add: new third sentence

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).

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values
Laboratory parameter "Hemoglobin"
Third bullet previously read:

If hemoglobin decreases ≥ 3.0 g/dL from Baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion.

Has been changed to read:

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.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values
Laboratory parameter "Absolute neutrophil count (ANC)"
Last bullet previously read:

Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.

Has been changed to read:

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.

Section 6.1.9 Cardiovascular Adjudication Committee
Previously read:

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

Has been changed to read:

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.

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

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

Appendix C. Study Activities
Activity "Other Central Lab tests" previously read:

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
Other Central Lab tests HIV Screening[v] Hepatitis B and C Screening Rheumatoid factor Anti-CCP antibodies	X					X[w]			X[w]								

Has been changed to read:

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
Other Central Lab tests HIV Screening[v] Hepatitis B[w] and C Screening Rheumatoid factor Anti-CCP antibodies	X																

Appendix C. Study Activities
Table note "w." previously read:

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 every 12 weeks. Retesting every 12 weeks is not necessary for subjects that have a history of HBV vaccine and HBs Ab+ and HBc Ab–.

Has been changed to read:

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.

Document Approval

Study M15554 - 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 - Amendment 7 - EudraCT 2016-004152-30 - 01Apr2020

Version: 1.0 **Date:** 10-Apr-2020 04:47:35 PM **Company ID:** 04102020-00F9F6845A81DA-00001-en

Signed by:	Date:	Meaning Of Signature:
PPD	01-Apr-2020 10:17:43 PM	Approver
	01-Apr-2020 11:17:47 PM	Approver
	02-Apr-2020 04:33:38 AM	Approver
	02-Apr-2020 01:00:26 P	Approver
	02-Apr-2020 02:26:51 PM	Approver
	02-Apr-2020 09:50:25 PM	Approver
	10-Apr-2020 04:47:33 P	Approver

1.0 Title Page

Clinical Study Protocol M15-554

A Phase 3, Randomized, Double-Blind, Study Comparing 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 Amendment 1

AbbVie Investigational Product:	ABT-494
Date:	27 February 2017
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:	AbbVie Inc.* Dept. R477, Bldg. AP31-3 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Contact:	PPD [redacted]

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	10 February 2017

The purpose of this amendment is to:

- Update Section 1.0, Title Page Sponsor/Emergency Contact Fax Number

  Rationale: *To ensure sites have the most current contact information for the Sponsor/Emergency Contact and to add the country code to the contact numbers.*
- Update Section 5.2.1, Inclusion Criteria

  Rationale: *To ensure subject safety.*
- Update Section 5.2.2, Exclusion Criteria

  Rationale: *To ensure subject safety.*
- Update Section 5.2.3.3, Prohibited Therapies

  Rationale: *To ensure subject safety.*
- Update Table 2, Clinical Laboratory Tests, footnote "f."

  Rationale: *To ensure those subjects in Japan with HBs Ab+ and/or HBc Ab+ at Screening have the testing performed as required per local guidelines.*
- Update Section 5.3.1.1, Study Procedures, Hepatitis Screening

  Rationale: *To ensure those subjects in Japan with HBs Ab+ and/or HBc Ab+ at Screening have the testing performed as required.*
- Update Section 6.1.5, Serious Adverse Event Reporting and Malignancy Reporting

  Rationale: *To ensure the country code was added to the Immunology Safety Team and Therapeutic Area Medical Director phone numbers.*
- Update Appendix C, Study Activities Table

  Rationale: *To ensure the correct footnote FSH testing was reflected (footnote "ff.").*

Rationale: *To ensure the correct subject questionnaires were completed at Week 2.*

Rationale: *To ensure the footnotes of "p." and "q." reflected a frequency of annually.*

Rationale: *To ensure those subjects in Japan with HBs Ab+ and/or HBc Ab+ at Screening have the necessary testing performed as required (footnote "w.").*

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

1.0 Title Page

Clinical Study Protocol M15-554

A Phase 3, Randomized, Double-Blind, Study Comparing 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 Amendments 1 and 2

AbbVie Investigational Product:	ABT-494
Date:	03 March 2017
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:	AbbVie Inc.* Dept. R477, Bldg. AP31-3 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Contact:	PPD

* 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

The purpose of this amendment is to:

- Update Section 1.2, Synopsis.
  Rationale: *To ensure subject safety.*
- Section 5.1, Overall Study Design and Plan: Description.
  Rationale: *To ensure subject safety.*
- Update Section 5.2.1, Inclusion Criteria.
  Rationale: *To ensure subject safety.*
- Update Section 5.2.2, Exclusion Criteria.
  Rationale: *To remove duplicate information.*
- Update Table 2, Clinical Laboratory Tests.
  Rationale: *To ensure subject safety.*
- Update Table 2, Clinical Laboratory Tests, footnote "h."
  Rationale: *To clarify the time until which protocol deviations should be reported.*
- Update Section 9.3, Subject Information and Consent.
  Rationale: *To clarify procedures on subject withdrawal related to optional exploratory samples.*
- Update Appendix C, Study Activities Table, footnote "s."
  Rationale: *To clarify the time until which protocol deviations should be reported.*

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

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 Amendments 1, 2, 2.01 (VHP Countries) and 3 and Administrative Change 1

AbbVie Investigational Product:	ABT-494
Date:	07 July 2017
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.* Dept. R477, Bldg. AP31-3 1 North Waukegan Road North Chicago, IL 60064 United States of America **For EU Countries:** AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany

Sponsor/Emergency Contact:	PPD

* 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

The purpose of this amendment is to:

- Update Section 1.0, Title Page

  Rationale: *To add the generic name of ABT-494.*

  Rationale: *To clarify the Sponsor for Non-EU Countries and EU Countries.*
- Update Section 1.2, Synopsis, Objectives

  Rationale: *To correct a typo in Period 1 Objective 1.*
- Update Section 1.2, Synopsis, Methodology

  Rationale: *To remove the possibility that subjects in screening may not be enrolled.*

  Rationale: *To clarify the subject non-responder criteria for rescue therapy and discontinuation.*

  Rationale: *To allow addition or modification of non-biologic DMARDs and oral corticosteroids.*
- Update Section 1.2, Synopsis, Main Exclusion

  Rationale: *To clarify the excluded inflammatory joint diseases.*
- Update Section 1.2, Synopsis, Safety

  Rationale: *To update a typographical error.*
- Update Section 1.3, List of Abbreviations and Definition of Terms

  Rationale: *To add the ADL and CTCAE abbreviations.*
- Update Section 3.2, Benefits and Risks

Rationale: *To add additional safety information for ABT-494.*

- Update Section 4.0, Study Objective

  Rationale: *To correct a typo in Period 1 Objective 1.*

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

  Rationale: *To remove the possibility that subjects in screening may not be enrolled.*

  Rationale: *To clarify the subject non-responder criteria for rescue therapy and discontinuation.*

  Rationale: *To allow addition or modification of non-biologic DMARDs and oral corticosteroids.*

  Rationale: *To clarify re-screening when a re-tested lab value remains exclusionary.*

  Rationale: *To clarify the procedures that are not required to be repeated for re-screening.*

  Rationale: *To clarify whether a PD visit is required following discontinuation of study drug.*

  Rationale: *To clarify the language for the follow-up visit.*

- Update Section 5.2.2, Exclusion Criteria

  Rationale: *To clarify HBV testing requirements for subjects if indicated by local requirements.*

  Rationale: *To delete the exclusion of clinically relevant or significant ECG abnormalities.*

  Rationale: *To delete the exclusion of moderate to severe congestive heart failure (New York Heart Associate class III or IV).*

  Rationale: *To clarify exclusion of those subjects that are previous recipients of organ transplants.*

  Rationale: *To delete the exclusion of history of demyelinating disease such as Multiple Sclerosis or neurologic symptoms suggestive of demyelinating disease (including myelitis).*

  Rationale: *To clarify the timeframe for the specified concomitant psoriasis treatments.*

Rationale: *To clarify the exclusion of oral or parenteral Traditional Chinese Medicines.*

Rationale: *To clarify the excluded inflammatory joint diseases.*

- Update Section 5.2.3.2, Permitted Background PsA/PsO Therapy

  Rationale: *To allow addition or modification of non-biologic DMARDs and oral corticosteroids.*

- Update Section 5.2.3.3, Prohibited Therapy

  Rationale: *To remove corticosteroids from the prohibited concomitant medications.*

  Rationale: *To clarify the Traditional Chinese Medication language.*

  Rationale: *To clarify prohibition of live vaccines during study.*

- Update Table 1, Examples of Commonly Used Strong CYP3A Inhibitors and Inducers

  Rationale: *To add Rifapentine as a strong CYP3A inducer.*

- Update Section 5.2.3.4, Rescue Therapy

  Rationale: *To clarify the subject non-responder criteria for rescue therapy and discontinuation and to allow addition or modification of non-biologic DMARDs and oral corticosteroids.*

- Update Section 5.2.4, Contraception Recommendations

  Rationale: *To remove the bullet point and align the text within the paragraph.*

  Rationale: *To update the allowable combined hormonal contraception.*

  Rationale: *To clarify the requirements of the vasectomized partner to confirm success of the procedure.*

  Rationale: *To clarify the contraception requirements for a woman on study who becomes surgically sterile or post-menopausal.*

- Update Section 5.3.1.1, Study Procedures, Informed Consent

  Rationale: *To clarify how the optional exploratory research and validation informed consent may be contained within the main consent form.*

- Update Section 5.3.1.1, Study Procedures, Physical Exam

  Rationale: *To clarify the baseline physical exam for the study.*

- Update Section 5.3.1.1, Study Procedures, 12-Lead Electrocardiogram (ECG)

  Rationale: *To clarify when a valid QTcF cannot be calculated and to clarify clinically significant findings.*
- Update Section 5.3.1.1, Study Procedures, Chest X-Ray (CXR)

  Rationale: *To permit either a radiologist or pulmonologist to perform assessment of the CXR.*
- Update Section 5.3.1.1, Study Procedures, Pregnancy Test

  Rationale: *To clarify serum pregnancy borderline test result language.*
- Update Section 5.3.1.1, Study Procedures, TB Testing/TB Prophylaxis

  Rationale: *To update typographical errors. To clarify the TB testing requirements. To add requirement to report AE if positive TB screen after study start. To clarify duration of TB prophylaxis. To add Rifapentine is not allowed for TB prophylaxis. To clarify the prophylactic treatment allowed for subjects with new evidence of latent TB.*
- Update Table 2, Clinical Laboratory Tests

  Rationale: *To clarify HBV testing requirements for subjects if indicated by local requirements in footnote "f." To clarify hs-CRP, CRP or serial procalcitonin tests reporting language in footnote "h."*
- Update Section 5.3.1.1, Study Procedures, Hepatitis Screening

  Rationale: *To clarify HBV DNA positive result language. To clarify HBV testing requirements for subjects if indicated by local requirements.*
- Update Figure 2, Criteria for HBV DNA PCR Qualitative Testing

  Rationale: *To update the Figure and to add the HBV testing requirements for subjects in Japan, or if indicated by local requirements.*
- Update Section 5.3.1.1, Study Procedures, Investigator Assessments

  Rationale: *To clarify the qualifications of the independent assessor.*
- Update Section 5.3.3.3, Additional Secondary Variables

  Rationale: *To clarify the time points when the additional secondary variables will be assessed. Clarified NRS for the Change from baseline in PGA and PtGA.*
- Update Section 5.4.1, Discontinuation of Individual Subjects

Rationale: *To clarify the subject non-responder criteria for rescue therapy and discontinuation.*

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

  Rationale: *To correct the section referenced.*

- Update Section 6.1.1.3, Adverse Events of Special Interest

  Rationale: *To update the adverse events of special interest that will be monitored during the study.*

- Update Section 6.1.2, Adverse Event Severity

  Rationale: *To update the classification of adverse events.*

- Update Section 6.1.4, Adverse Event Collection Period

  Rationale: *To clarify when a Supplemental AE eCRF should be completed.*

- Update Section 6.1.7, Toxicity Management

  Rationale: *To clarify and refer to Section 5.5.4, Selection and Timing of Dose for Each Subject, for study drug interruption guidelines. To update serious gastrointestinal events as gastrointestinal perforation. To clarify the ECG abnormality discontinuation requirements. To clarify the management of select laboratory abnormalities.*

- Update Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values

  Rationale: *To update the AST or ALT, serum creatinine and Creatine Phosphokinase toxicity management guidelines.*

- Update Section 8.1.5.3, Analysis of Laboratory, Vital Sign and ECG Data

  Rationale: *To update the classification of laboratory abnormalities*

- Update Section 8.1.6, Pharmacokinetic and Exposure-Response Analyses

  Rationale: *To clarify the analysis of covariates on exposure-response relationships.*

- Update Appendix C, Study Activities

  Rationale: *To update the number of days for the 30 day follow-up visit/call.*

  Rationale: *To update the superscript "i." for the ECG at Screening and Wk 68 to Wk 140.*

Rationale: *To update the superscript "s" to clarify hs-CRP, CRP or serial procalcitonin tests reporting language.*

Rationale: *To update the superscript from "z" to "ee" for the subject questionnaires (HAQ-DI, Patient-Pain, PtGA-disease activity, SF-36, EQ-5D-5L, FACIT-F, WPAI, BASDAI).*

Rationale: *To add superscript "z" for the following activities: SAPS, BSA Psoriasis, PASI, sIGA.*

Rationale: *To clarify the follow-up requirement in footnote "b."*

Rationale: *To clarify HBV testing requirements for subjects if indicated by local requirements in footnote "w."*

Rationale: *To delete the Dispense Study Drug and Subject Diary "X" at Week 2.*

Rationale: *To update footnote "z." with sIGA and to add clarification.*

Rationale: *To update footnote "cc." and "dd." with the subject non-responder criteria for rescue therapy and discontinuation.*

- Update Appendix D, Study Activities – Optional Samples for Exploratory Research or Validation Studies

  Rationale: *To update the number of days for the Wk 56, Wk 68 to Wk 140 and Wk 152 or PD visits.*

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

  Rationale: *To delete this appendix as it is no longer applicable.*

- Update Appendix G, Local Requirements

  Rationale: *To remove erroneous reference to subcutaneous study drug and identify the correct inclusion criterion.*

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

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 Change 1 and Amendments 1, 2, 2.01 (VHP Countries), 3, and 4

AbbVie Investigational Product:	ABT-494
Date:	23 March 2018
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 Bldg. AP31-2 North Chicago, IL 60064 United States of America **For EU Countries:** AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany

ABT-494
M15-554 Protocol Amendment 4
EudraCT 2016-004152-30

Sponsor/Emergency Contact:	PPD

* 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

The purpose of this amendment is to:

- Apply administrative changes throughout protocol

  Rationale: *Revised text to improve consistency and readability, and/or provide clarification.*
- Update Section 1.0, Title Page

  Rationale: *To update the Sponsor information for Non-EU Countries.*

  Rationale: *Sponsor 24 hour emergency contact number already available in Section 6.1.4; added here to facilitate location in an emergency situation.*
- Update Section 1.2, Synopsis, Methodology

  Rationale: *To clarify that stratification will be done by the number of prior biologics a subject has failed (had an inadequate response to).*
- Update Section 5.1, Overall Study Design and Plan: Description

  Rationale: *To add "30" as it was omitted in error.*

  Rationale: *To clarify that stratification will be done by the number of prior biologics a subject has failed (had an inadequate response to).*

  Rationale: *To stop annual TB testing after discontinuation of study drug as the increased risk of TB associated with immune suppression is no longer present after study drug discontinuation.*

  Rationale: *To include trigger point, tender point, intra-bursa corticosteroid injections as options for rescue therapy.*

- Update Section 5.2.1, Inclusion Criteria

  Rationale: *To decrease the required washout period to the lower end of the range of 5 half-lives for both secukinumab and usetekinumab in order to minimize the rates of flare during washout while ensuring subject safety. The half-life of secukinumab is 22 – 31 days; 5 half-lives is equivalent to 15.7 – 22 weeks. The half-life of ustekinumab is 14.9 – 45.6 days; 5 half-lives is equivalent to 10 – 32.5 weeks.*

  Rationale: *To remove requirement for male contraception from Inclusion Criterion 11. Based on the recently completed embryo fetal development study in rats, a NOEL (no observed effect level) was confirmed at 1.5 mg/kg/day. Upadacitinib is not genotoxic, but is teratogenic in rats and rabbits. Using the NOEL identified in rats compared to the highest upadacitinib dose (30 mg QD) being evaluated in this clinical trial there is at least a 276-fold exposure margin for potential fetal exposure (for 15 mg QD, margin was 662-fold). Therefore, there is judged to be no product risk associated with administration of upadacitinib to male partners of females of childbearing potential. As a result, males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study.*

- Update Section 5.2.2, Exclusion Criteria

  Rationale: *To specify only enrollment in another interventional clinical study is prohibited as concomitant enrollment in non-interventional studies could be permitted.*

  Rationale: *To specify interpretation of an indeterminate result for beta-D-glucan.*

  Rationale: *To clarify that only prior organ transplant requiring current immunosuppressive therapy is exclusionary, as if the need for immunosuppression has ended there is no risk of additive immunosuppression with addition of the study drug.*

  Rationale: *To define "NMSC" acronym.*

  Rationale: *To remove 'prohibited' as these concomitant medications are not prohibited for the duration of the study and may be used after Week 16 and to clarify and expand on therapies which are permitted and prohibited prior to*

the baseline visit as many therapies may have an effect on efficacy assessments.

Rationale: *To add fumarates to the list of psoriasis treatments prohibited prior to baseline and specify the timeframe within which it is prohibited, as fumarates may affect baseline skin assessments.*

Rationale: *To add laser therapy to the list of psoriasis light treatments prohibited within 2 weeks of baseline, as laser therapy may also affect baseline skin assessments.*

Rationale: *To clarify that all topical psoriasis treatments including medicated shampoos are prohibited within 2 weeks of baseline. To remove redundant exception of low potency topical corticosteroids as it is listed.*

Rationale: *Removed 'shampoos that contain no corticosteroid' as it is redundant to edited statement that all topical treatments including medicated shampoos are prohibited within 2 weeks of baseline.*

Rationale: *To add urea and salicylic acid to the list of prohibited ingredients in emollients.*

Rationale: *To clarify that topical anti-itch treatments are permitted as psoriasis treatment.*

Rationale: *To clarify that use of opioid analgesics except for the combination of acetaminophen and codeine or acetaminophen and hydrocodone are not permitted within 1 week of the Baseline visit as outlined in Inclusion Criterion 9. To exclude use of inhaled marijuana within 2 weeks prior to baseline visit due to an increased risk for aspergillosis infection.*

Rationale: *To align Exclusion Criterion 13 with Section 5.2.4 (contraception recommendations) and clarify that pregnancy is not permitted for at least 30 days after last dose of study drug.*

Rationale: *To remove Exclusion Criterion 14. Based on the recently completed embryo fetal development study in rats, a NOEL (no observed effect level) was confirmed at 1.5 mg/kg/day. Upadacitinib is not genotoxic, but is teratogenic in rats and rabbits. Using the NOEL identified in rats compared to the highest upadacitinib dose (30 mg QD) being evaluated in this clinical trial there is at least a 276-fold exposure margin for potential fetal exposure (for 15 mg QD, margin was 662-fold). Therefore, there is judged to be no*

product risk associated with administration of upadacitinib to male partners of females of childbearing potential. As a result, males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study and the exclusion criteria is removed as there is no risk associated with upadacitinib related to fathering a child or sperm donation.

- Update Section 5.2.3.2, Permitted Background PsA/PsO Therapy

  Rationale: *To remove reference to PsA and PsO as this section applies to all background therapies given for any reason during the study.*

  Rationale: *To clarify that stability of background DMARDs is preferred, but not mandatory as there could be situations where changes are required to ensure subject safety.*

  Rationale: *To clarify that stability of background NSAIDs, analgesics, and corticosteroids is preferred, but not mandatory as there could be situations where changes are required to ensure subject safety.*

  Rationale: *To clarify that if not taking NSAIDs, acetaminophen/paracetamol, low-potency opiates (tramadol or combination of acetaminophen with codeine or hydrocodone), oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), it is preferred, but not mandatory, that these not be initiated as it is expected that some subjects may have adverse events which require use or modification of such therapies.*

  Rationale: *To include trigger point, tender point, intra-bursa corticosteroid injection as options for rescue therapy.*

  Rationale: *Updated language for permitted shampoos to align with revised exclusion criterion.*

  Rationale: *Updated emollients to align with revised exclusion criterion.*

  Rationale*: To allow the use of any type of PsO therapy after Week 16 assessments are performed, with adherence to permitted non-biologic DMARD guidelines.*

- Update Section 5.2.3.3, Prohibited Therapy

  Rationale: *To specifically prohibit epidural corticosteroid injections.*

Rationale: *To exclude use of inhaled marijuana within 2 weeks prior to the baseline visit due to an increased risk for aspergillosis infection.*

- Update Section 5.2.3.4, Rescue Therapy

  Rationale: *To include trigger point, tender point, intra-bursa corticosteroid injection as options for rescue therapy.*

- Update Section 5.2.4, Contraception Recommendations

  Rationale: *To clarify the surgical procedures which are considered adequate to prevent pregnancy.*

  Rationale: *To correct the typographical error in units for FSH.*

  Rationale: *To clarify that all requirements for pregnancy testing in women of childbearing potential must be followed, not only the serum pregnancy test during the screening period.*

  Rationale: *Section updated to provide new data from animal studies which demonstrate there is no effect of upadacitinib on male reproduction and remove contraception requirements for male study subjects. Based on the recently completed embryo fetal development study in rats, a NOEL (no observed effect level) was confirmed at 1.5 mg/kg/day. Upadacitinib is not genotoxic, but is teratogenic in rats and rabbits. Using the NOEL identified in rats compared to the highest upadacitinib dose (30 mg QD) being evaluated in this clinical trial there is at least a 276-fold exposure margin for potential fetal exposure (for 15 mg QD, margin was 662-fold). Therefore, there is judged to be no product risk associated with administration of upadacitinib to male partners of females of childbearing potential. As a result, males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study.*

- Update Section 5.3.1.1, Study Procedures, Chest X-Ray (CXR)

  Rationale: *To clarify that only one TB risk factor as identified on the TB risk assessment form is required for chest x-ray to be performed annually.*

- Update Section 5.3.1.1, Study Procedures, Pregnancy Test

  Rationale: *To end pregnancy testing in subjects who have a change in their child-bearing potential status and are no longer at risk of pregnancy.*

- Update Section 5.3.1.1, Study Procedures, TB Testing/TB Prophylaxis

  Rationale: *To provide interpretation of the TB risk assessment form.*

  Rationale: *To require all subjects to have a QuantiFERON-TB Gold Test performed by the central laboratory during screening even if a local IGRA or PPD test has been performed within 90 days, except in the case where a QuantiFERON-TB Gold Test cannot be performed by the central laboratory.*

  Rationale: *To permit both use of the central laboratory and local laboratory for the QuantiFERON-TB Gold test if the initial screening test is negative and annual testing becomes positive by the central laboratory in a subject at low-risk of TB as a positive result in this setting may indicate sampling error or artifact introduced during the shipping process.*

  Rationale: *It is expected to perform the QuantiFERON-TB Gold test through the central laboratory unless it is not possible to do so or a subject has had a prior positive test.*

  Rationale: *To reflect that a positive TB test by any testing modality will be considered positive for the purposes of the study as this is the most conservative interpretation and will maintain subject safety.*

  Rationale: *To permit both use of the central laboratory and local laboratory for the QuantiFERON-TB Gold test if the initial test performed by the central laboratory is indeterminate as an indeterminate result may indicate sampling error or artifact introduced during the shipping process.*

  Rationale: *To remove the 1 year limitation for enrollment of subjects with prior history of latent TB with documentation of a full course of anti-TB therapy as a 1 year period is arbitrary and a longer time since TB prophylaxis is not known to increase risk of active TB.*

  Rationale: *To remove the requirement for consultation with the TA MD for subjects with greater than 1 year since completion of TB prophylaxis as the investigator can safely determine risk of new exposure based on history, physical, and a subject's responses to the Latent TB risk factor questionnaire.*

  Rationale: *To mandate prophylactic treatment for latent TB and specify the minimum amount of time a subject must be on prophylactic treatment to align with CDC standards for prophylaxis with isoniazid.*

- Update Table 2, Clinical Laboratory Tests

Rationale: *To clarify that a separate tube is required for INR testing and that this testing is not performed on blood from the tube drawn for ALT and/or AST.*

Rationale: *To explicitly permit use of a local laboratory if results are not interpretable.*

- Update Section 5.3.1.1, Study Procedures, Hepatitis Screening

  Rationale: *To provide the full term in addition to the abbreviations.*

  Rationale: *To clarify when HBV DNA PCR testing is required prior to enrollment.*

  Rationale: *HBV DNA PCR is required in the case of a positive test for HBs Ab + without documentation of vaccination, if a local requirement for a positive test for HBs Ab, or if a positive test for HBc Ab.*

  Rationale: *To clarify the conditions at screening for which the HBV DNA PCR test should be performed every 12 weeks for Japan or where mandated by local requirements.*

  Rationale: *Deleted text on guidance for evaluation of subjects who develop a positive HBV DNA PCR test result as this guidance is provided in Table 4.*

- Update Figure 2, Interpretation and Management of HBV Serologic Test Results

  Rationale: *To clarify in the figure title that the figure provides guidance on interpretation of testing, when to perform HBV PCR testing, and when to permit a subject to enroll.*

  Rationale: *To clarify when HBV DNA PCR testing is required prior to enrollment.*

- Update Section 5.3.1.1, Study Procedures, Randomization and Drug Assignment

  Rationale: *To clarify that stratification will be done by the number of prior biologics a subject has failed (had an inadequate response to).*

- Update Section 5.3.1.1, Study Procedures, Investigator Assessments

  Rationale: *To specify the types of assessors appropriate for completion of each assessment.*

- Update Section 5.4.1, Discontinuation of Individual Subjects

Rationale: *To additionally allow the AbbVie TA MD to determine if subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation.*

Rationale: *To stop annual TB testing after discontinuation of study drug as the increased risk of TB associated with immune suppression is no longer present after study drug discontinuation.*

- Update Section 5.5.3, Method of Assigning Subjects to Treatment Group

  Rationale: *To clarify that stratification will be done by the number of prior biologics a subject has failed (had an inadequate response to).*

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

  Rationale: *Text removed as redundant to the preceding sentence.*

- Update Section 6.1.1.3, Adverse Events of Special Interest

  Rationale: *Updated for clarification and consistency across upadacitinib programs and to represent AESIs based on upadacitinib and other JAK class studies.*

  Rationale: *To remove subtypes of malignancy as all malignancies will be captured under the more general category of malignancy (all types).*

  Rationale: *To remove rhabdomyolysis/myopathy, as there is no evidence to support an increased risk for rhabdomyolysis or myopathy with upadacitinib or other JAK inhibitors. CPK elevations will continue to be monitored as AESI.*

  Rationale: *To add embolic and thrombotic events as AESI, based on data reported for JAK inhibitors.*

  Rationale: *To remove cardiac arrhythmias as AESI, as there is no evidence to support an increased risk for cardiac arrhythmias with upadacitinib. Studies with exposure-response analyses to evaluate the QT prolongation potential for upadacitinib demonstrated that upadacitinib does not prolong the QT interval at the doses being evaluated in this study or under the highest (or worst-case) potential clinical exposures. Upadacitinib has also been tested in safety pharmacology assays to assess effects on the cardiovascular system with no effects on electrophysiological parameters. Subjects will continue to be*

carefully and closely monitored for cardiovascular events throughout the study.

- Update Section 6.1.2, Adverse Event Severity

  Rationale: *To clarify instructions to investigators for grading of severe AEs for which guidance for the specific events is not available.*

- Update Section 6.1.4, Adverse Event Collection Period

  Rationale: *To add non-cardiac non-CNS embolic events and non-cardiac non-CNS thrombotic events to the AEs requiring a supplemental AE eCRF as such events have been observed in the JAK class.*

- Update Section 6.1.6, Pregnancy

  Rationale: *Males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study.*

- Update Section 6.1.7, Toxicity Management

  Rationale: *To clarify that subjects with active TB will not be permitted to restart study drug.*

- Update Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values

  Rationale: *To improve readability and provide clarity on the management for AST and ALT abnormalities, including INR testing specifics and interruption vs. discontinuation of study drug when toxicity management criteria are met as it may be possible to safely restart study drug in selected subjects at a later timepoint.*

  Rationale: *To account for situations in which an alternative etiology of ALT or AST elevations may exist and outline appropriate steps to take.*

  Rationale: *To clarify that the eCRF is only required for confirmed ALT or AST elevations > 3 ULN.*

  Rationale: *To provide direction on management of subjects with potential HBV reactivation.*

- Update Section 7.0, Protocol Deviations

  Rationale: *To update alternative contact.*

- Update Section 8.1.4.1, Primary Efficacy Variable

  Rationale: *Weight subgroup removed as BMI is considered to be more informative and the weight subgroup is not expected to provide additive understanding of therapeutic effect.*

- Update Section 8.1.4.2, Key Secondary Efficacy Variables

  Rationale: *To reflect the change in method utilized for pairwise comparisons between dose groups to MMRM.*

- Update Section 8.1.4.5, Imputation Methods

  Rationale: *To replace PMM with a more interpretable MNAR model.*

- Update Section 8.1.5.1, General Considerations

  Rationale: *To allow analysis of both visit value and change from baseline; details will be provided in the SAP.*

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

  Rationale: *To update the planned analysis to match the revised AESI list in Section 6.1.1.3.*

- Update Section 8.1.5.3, Analysis of Laboratory, Vital Sign, and ECG Data

  Rationale: *To allow analysis of both visit value and change from baseline; details will be provided in the SAP.*

  Rationale: *Update definitions of shift table categories that facilitate clinical interpretation.*

  Rationale: *To clarify both summary and listings will be provided.*

- Update Section 8.1.6, Randomization Methods

  Rationale: *To clarify that stratification will be done by the number of prior biologics a subject has failed (had an inadequate response to).*

- Update Appendix B, List of Protocol Signatories

  Rationale: *To update the list of protocol signatories.*

- Update Appendix C, Study Activities

  Rationale: *To clarify that if one or more TB risk factors is identified on the TB risk assessment form a chest x-ray is required annually.*

  Rationale: *There is no evidence suggesting that obtaining a chest x-ray on a more than annual basis in a population at high risk of TB is of benefit.*

Clarification that a chest x-ray in a subject who prematurely discontinues study drug should not be done unless they are near the annual testing requirement decreases radiation exposure.

Rationale: *To add if a urine pregnancy test is positive at any time during the study, a serum pregnancy test must be collected in order to confirm pregnancy.*

Rationale: *There is no evidence suggesting that obtaining repeat TB testing on a more than annual basis is of benefit to detect active or latent TB.*

Rationale: *To clarify the visits for PK collection in the footnote.*

- Update Appendix G, Local Requirements

Rationale: *To clarify on Inclusion Criterion 11 that the combination of two highly effective methods would be acceptable in addition to 1 highly effective method and 1 effective method of contraception.*

Rationale: *To remove requirement for male contraception from Inclusion Criterion 11. Based on the recently completed embryo fetal development study in rats, a NOEL (no observed effect level) was confirmed at 1.5 mg/kg/day. Upadacitinib is not genotoxic, but is teratogenic in rats and rabbits. Using the NOEL identified in rats compared to the highest upadacitinib dose (30 mg QD) being evaluated in this clinical trial there is at least a 276-fold exposure margin for potential fetal exposure (for 15 mg QD, margin was 662-fold). Therefore, there is judged to be no product risk associated with administration of upadacitinib to male partners of females of childbearing potential. As a result, males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study.*

Rationale: *To correct the typographical error in FSH units.*

Rationale: *Removed erroneous reference to subcutaneous study drug, as this study does not include a subcutaneous study drug.*

Rationale: *To correct a typographical error.*

Rationale: *To remove Canada-specific contraception recommendations for males as country-specific requirements no longer apply. Based on the recently completed embryo fetal development study in rats, a NOEL (no observed effect level) was confirmed at 1.5 mg/kg/day. Upadacitinib is not genotoxic, but is teratogenic in rats and rabbits. Using the NOEL identified in rats compared*

to the highest upadacitinib dose (30 mg QD) being evaluated in this clinical trial there is at least a 276-fold exposure margin for potential fetal exposure (for 15 mg QD, margin was 662-fold). Therefore, there is judged to be no product risk associated with administration of upadacitinib to male partners of females of childbearing potential. As a result, males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study.

Rationale: *To correct the typographical error in FSH units.*

Rationale: *Removed erroneous reference to subcutaneous study drug, as this study does not include a subcutaneous study drug.*

Rationale: *To remove South Korea-specific contraception recommendations for males as country-specific requirements no longer apply. Based on the recently completed embryo fetal development study in rats, a NOEL (no observed effect level) was confirmed at 1.5 mg/kg/day. Upadacitinib is not genotoxic, but is teratogenic in rats and rabbits. Using the NOEL identified in rats compared to the highest upadacitinib dose (30 mg QD) being evaluated in this clinical trial there is at least a 276-fold exposure margin for potential fetal exposure (for 15 mg QD, margin was 662-fold). Therefore, there is judged to be no product risk associated with administration of upadacitinib to male partners of females of childbearing potential. As a result, males are no longer required to use contraception when participating in this upadacitinib clinical trial unless required due to the risk of a concomitant medication taken during the study.*

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

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 Change 1, 2 and Amendments 1, 2, 2.01 (VHP Countries), 3, 4 and 5

AbbVie Investigational Product:	ABT-494
Date:	14 January 2019
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 Bldg. AP31-2 North Chicago, IL 60064 United States of America **For EU Countries:** AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany

ABT-494
M15-554 Protocol Amendment 5
EudraCT 2016-004152-30

Sponsor/Emergency Contact:

* 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

The purpose of this amendment is to:

- Apply administrative changes throughout protocol

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

  Rationale: *To specify pre-determined stratification enrollment limits related to extent of psoriasis involvement and prior failure of more than 1 biologic DMARD which ensure a balanced study population that is comparable to similar studies. The stratification enrollment limit on BSA will also ensure a sufficient number of subjects in the stratum BSA ≥ 3% to power key skin-related efficacy endpoints (assessed on the stratum only). There is no change to the planned study conduct, data collection and analysis.*
- Update Section 5.1, Overall Study Design and Plan: Description

  Rationale: *To specify pre-determined stratification enrollment limits related to extent of psoriasis involvement and prior failure of more than 1 biologic DMARD which ensure a balanced study population that is comparable to similar studies. The stratification enrollment limit on BSA will also ensure a sufficient number of subjects in the stratum BSA ≥ 3% to power key skin-*

related efficacy endpoints (assessed on the stratum only). There is no change to the planned study conduct, data collection and analysis.

- Update Section 5.1, Overall Study Design and Plan: Description, Discontinuation of Study Drug and Continuation of Study Participation (Period 1 and Period 2)

  Rationale: *Section 5.2.3.1 refers to Prior Therapy and is an incorrect reference. The parameters provided for mandatory discontinuation from study drug at Week 36 are complete as written and reference to another section of the protocol is unnecessary.*

- Update Section 5.2.2, Exclusion Criteria, The Rationale for the Exclusion Criteria

  Rationale: *To correct the associations between rationale and exclusion criteria.*

- Update Section 5.3.1.1, Study Procedures, Pregnancy Test

  Rationale: *Requirement for male contraception was removed in Amendment 3, therefore discussion of pregnancy avoidance for female partners of male subjects is no longer required.*

- Update Section 5.3.1.1, Study Procedures, TB Testing/TB Prophylaxis

  Rationale: *To permit both use of the central laboratory and local laboratory for the QuantiFERON-TB Gold test at initial screening in a subject at low risk of TB as a positive result in this setting may indicate sampling error or artifact introduced during the shipping process and may result in unnecessary use of INH.*

  Rationale: *Replaced text pertaining to retesting of a positive QuantiFERON-TB Gold in low-risk subjects at annual screening with text above in same section to permit retesting at both initial screening and annually in low-risk subjects who have a positive screening test, as this paragraph only pertains to annual testing.*

  Rationale: *To expressly permit use of an equivalent IGRA blood test for TB screening.*

- Update Table 2, Clinical Laboratory Tests, Footnote f

Rationale: *To correct the language in this section so that it is consistent with Section 6.1.7 Toxicity Management, Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values and Section 5.3.1.1 Study Procedures, Section Hepatitis Screening, Subsection Hepatitis B.*

- Update Section 5.3.1.1, Study Procedures, Randomization and Drug Assignment

  Rationale: *To specify pre-determined stratification enrollment limits related to extent of psoriasis involvement and prior failure of more than 1 biologic DMARD which ensure a balanced study population that is comparable to similar studies. The stratification enrollment limit on BSA will also ensure a sufficient number of subjects in the stratum BSA ≥ 3% to power key skin-related efficacy endpoints (assessed on the stratum only). There is no change to the planned study conduct, data collection and analysis*

- Update Section 5.5.3, Method of Assigning Subjects to Treatment Group

  Rationale: *To specify pre-determined stratification enrollment limits related to extent of psoriasis involvement and prior failure of more than 1 biologic DMARD which ensure a balanced study population that is comparable to similar studies. The stratification enrollment limit on BSA will also ensure a sufficient number of subjects in the stratum BSA ≥ 3% to power key skin-related efficacy endpoints (assessed on the stratum only). There is no change to the planned study conduct, data collection and analysis.*

- Update Section 5.5.7, Drug Accountability

  Rationale: *Changed text to update the drug accountability requirements according to the revised sponsor guidelines.*

- Update Section 6.1.5, Serious Adverse Event Reporting and Malignancy Reporting

  Rationale: *To correct the language in this section by removing reference to SUSAR reporting in the USA as SUSAR reporting requirements only apply to EU countries.*

- Update Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values

  Rationale: *To clarify the listed symptoms must be new from baseline in order to meet the AST or ALT toxicity management criterion.*

Rationale: *Multiple hepatic eCRF are available to the site for completion; sites should select the eCRF(s) relevant to the specific situation.*

Rationale: *Multiple renal eCRF are available to the site for completion; sites should select the eCRF(s) relevant to the specific situation.*

- Update Section 7.0, Protocol Deviations

  Rationale: *Update the address for Barbara Cristofanelli*

- Update Appendix B, List of Protocol Signatories

  Rationale: *To update the list of protocol signatories.*

- Update Appendix C, Study Activities, Footnote w

  Rationale: *To correct the language in this section so that it is consistent with Section 6.1.7 Toxicity Management, Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values and Section 5.3.1.1 Study Procedures, Section Hepatitis Screening, Subsection Hepatitis B. Guidance for evaluation of subjects who develop a positive HBV DNA PCR test result is provided in Table 4.*

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

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 Change 1, 2 and Amendments 1, 2, 2.01 (VHP Countries), 3, 4, 5, and 6

AbbVie Investigational Product:	ABT-494
Date:	04 October 2019
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 Bldg. AP31-2 North Chicago, IL 60064 United States of America **For EU Countries:** AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany

ABT-494
M15-554 Protocol Amendment 6
EudraCT 2016-004152-30

Sponsor/Emergency Contact:	PPD [redacted]

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	10 February 2017
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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

The purpose of this amendment is to:

- Apply administrative changes throughout protocol

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

  Update Section 1.2, Synopsis, Efficacy

  Rationale: *To update FACIT-F placement in the multiplicity adjusted endpoints to reflect revised power calculations based on new data which became available during the conduct of the study.*

  Rationale: *To correct description of PsARC to reflect that it is a binary endpoint.*

  Rationale: *To correct description of Health Resource Utilization.*

  Rationale: *To add the proportion of subjects achieving MDA at all timepoints for which data is collected.*
- Update Section 1.3 List of Abbreviations and Definition of Terms

  Rationale: *Added definition of PsO.*
- Update Section 3.2 Benefits and Risks, 2nd paragraph

Rationale: *Update safety information regarding thromboembolic events and embryofetal effects.*

- Update Section 5.2.3.3 Prohibited Therapy, Table 1

  Rationale: *Rifampicin is another commonly used name for rifampin.*

- Update Section 5.3.1.1, Study Procedures, 12-Lead Electrocardiogram (ECG)

  Rationale: *Removed as Sponsor does not require each signed original ECG to be monitored by the site monitor.*

- Update Section 5.3.1.1, Study Procedures, Chest X-Ray (CXR)

  Rationale: *To clarify which subjects are required to have annual chest x-rays.*

- Update Section 5.3.1.1, Study Procedures, TB Testing/TB Prophylaxis

  Rationale: *Rifampicin is another commonly used name for rifampin.*

  Rationale: *Clarified wording regarding initiation and monitoring of prophylactic latent TB treatment during the study.*

- Update Section 5.3.3.2, Key Secondary Variables

  Rationale: *To update FACIT-F placement in the multiplicity adjusted endpoints to reflect revised power calculations based on new data which became available during the conduct of the study.*

- Update Section 5.3.3.3, Additional Variables

  Rationale: *To clarify that variables included in this section are distinct from the key secondary variables.*

  Rationale: *To correct description of PsARC to reflect that it is a binary endpoint.*

  Rationale: *To correct description of Health Resource Utilization.*

  Rationale: *To add the proportion of subjects achieving MDA at all timepoints for which data is collected.*

- Update Section 5.4.1 Discontinuation of Individual Subjects

  Rationale: *To clarify that subjects may request withdrawal from both study drug or the study.*

- Update Section 5.6.1, Discussion of Study Design and Choice of Control Groups

Rationale: *To align with changes made in Section 5.3.3.3.*

- Update Section 6.1.2 Adverse Event Severity

  Rationale: *To specify the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version to be used.*

- Update Section 6.1.7 Toxicity Management

  Rationale: *To add management guidelines surrounding herpes zoster, skin cancer screening, and thrombosis to align with Rinvoq® labeling. To add guidance for testing and management related to muscle-related symptoms.*

- Update Table 4, Specific Toxicity Management Guidelines for Abnormal Laboratory Values

  Rationale: *To update AST/ALT toxicity management guidelines to provide additional guidance to investigators regarding management of subjects with AST/ALT elevations.*

- Update Section 8.1.4.3 Additional Efficacy Variables

  Rationale: *To align with changes made in Section 5.3.3.3.*

- Update Section 8.1.4.4 Multiplicity Control for the Primary and Key Secondary Endpoints

  Rationale: *The multiplicity adjustment for secondary endpoints has been updated and the specified methodology no longer applies.*

- Update Section 8.1.5.1 General Considerations

  Rationale: *While ECGs remain part of the safety evaluation during the study, specific ECG analyses are not planned.*

- Update Section 8.1.5.3 Analysis of Laboratory and Vital Sign Data

  Rationale: *While ECGs remain part of the safety evaluation during the study, specific ECG analyses are not planned.*

  Rationale: *Clarified how summary statistics of laboratory and vital sign data will be presented and categorized and changed categorization of laboratory data from low, normal and high to National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) grades.*

- Update Appendix B, List of Protocol Signatories

  Rationale: *To update the list of protocol signatories.*

- Update Appendix C, Study Activities, Footnotes k and gg

  Rationale: *To clarify which subjects are required to have annual chest x-rays.*

  Rationale: *To specify that only blood chemistry and hematology are to be collected at the 30 day follow-up visit to monitor for any new laboratory abnormalities or resolution of existing abnormalities.*

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

1.0 Title Page

Statistical Analysis Plan

Study 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*

Date: 12 Apr 2018

Version 1.0

2.0 Table of Contents

List of Tables

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the Data and Statistical Science Department for upadacitinib Study M15-554. It provides details to further elaborate statistical methods as outlined in the protocol. Pharmacokinetic and biomarker analyses will be performed separately and are not in the scope of this SAP.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Study 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 biologic DMARDs (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 biologic DMARDs.

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.

4.2 Overall Study Design and Plan

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 active 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.

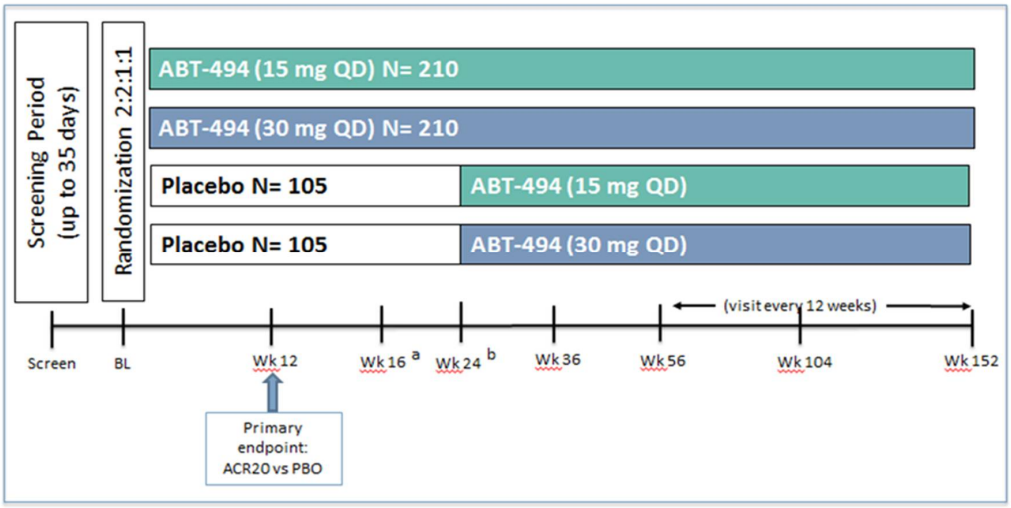
Subjects who meet eligibility criteria will be randomized in a 2:2:1:1 ratio using an Interactive Response Technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: Upadacitinib 15 mg QD, N = 210 (Day 1 to Week 24) → Upadacitinib 15 mg QD (Week 24 and thereafter)
- Group 2: Upadacitinib 30 mg QD, N = 210 (Day 1 to Week 24) → Upadacitinib 30 mg QD (Week 24 and thereafter)
- Group 3: Placebo, N = 105 (Day 1 to Week 24) → Upadacitinib 15 mg QD (Week 24 and thereafter)
- Group 4: Placebo, N = 105 (Day 1 to Week 24) → Upadacitinib 30 mg QD (Week 24 and thereafter)

Randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD (Yes or No), and number of prior failed 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.

A schematic of the overall study design is shown in Figure 1 below. For a more detailed description of the study design, refer to Section 5.0 of the most up-to-date version of the study protocol.

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 of the most up-to-date version of the study protocol.

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

4.3 Sample Size

The planned total 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 a two-sided significance level of 0.025 and accounting for a 10% dropout rate.

4.4 Week 24 Analysis and Data Base Lock

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 (Period 1), study sites and subjects will remain blinded until all subjects have reached Week 56.

4.5 Data Monitoring Committee (DMC) Activities

An independent external Data Monitoring Committee (DMC) is used to review unblinded safety data at regular intervals during the conduct of the study. The DMC will provide recommendation to an AbbVie Point of Contact on whether to continue, modify, or terminate studies after each review. When needed, high-level unblinded efficacy data may also be requested by the DMC and be reviewed so that the DMC can assess benefit:risk of any emerging safety differences.

5.0 Analysis Populations and Analysis Windows

5.1 Analysis Populations

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.

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 any major protocol deviations determined to have a potential impact on the primary efficacy endpoint up to Week 12 in Period 1 of the study. Additional analysis of the primary efficacy endpoint will be conducted on the Per Protocol analysis set, in order to evaluate the impact of protocol deviations.

Protocol deviations with potential to affect the primary efficacy endpoint (key ICH deviations and other clinically significant non-ICH deviations) will be identified prior to the Week 24 database lock.

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 will be analyzed "as treated," regardless of the treatment randomized. "As treated" is determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period.

5.2 Analysis Windows

Definition of Study Days (Days Relative to the First Dose of Study Drug)

Study Days are calculated for each collection date relative to the date of the first dose of study drug. It is defined as the number of days between the date of the first dose of study drug and the collection date. Study days are negative values when the collection date of interest is prior to the first study drug dose date. Study days are positive values when the collection date of interest is on or after the first study drug dose date. The day of the first dose of study drug is defined as Study Day 1, while the day prior to the first study drug dose is defined as Study Day –1 (there is no Study Day 0). Study days are used to map actual study visits to the protocol-specified study visits.

Definition of Analysis Windows

The following rules will be applied to assign actual subject visits to protocol-specified visits. For each protocol-specified study visit, a target study day will be identified to represent the corresponding visit along with a window around the target day. Windows will be selected in a non-overlapping fashion so that a collection date does not fall into multiple visit windows. If a subject has two or more actual visits in one visit window, the visit closest to the target day will be used for analysis. If two visits are equidistant from the target day, then the later visit will be used for analysis.

The visit window and the target study day for each protocol-specified visit in Period 1 are displayed in Table 1 to Table 5 (depending on the different visit schedules of different endpoints). Visit windows for protocol-specified visits in Period 2 are defined similarly.

Table 1. Analysis Windows for Efficacy Analysis for Period 1 (for ACR Components, TJC28, SJC28, ESR and Derived Endpoints[a]) and Safety Analysis for Period 1 (for Lab Values [Clinical Chemistry, Hematology, Urinalysis] and Vital Signs/Weight)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
2	2	15	22
4	23	29	43
8	44	57	71
12	72	85	99
16	100	113	127
20	128	141	155
24	156	169	Min (183, first dose date from Week 24 dispensed kit)
28	Min (183, first dose date from Week 24 dispensed kit) + 1	197	211
32	212	225	239
36	240	253	281
44	282	309	351
56	352	393	435

a. ACR20/50/70 response rates, DAS28 (CRP), DAS28 (ESR), PsARC, DAPSA, proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35).

b. Day of first dose of study drug.

Table 2. Analysis Windows for Efficacy Analysis for Period 1 (for SF-36, EQ-5D-5L, FACIT-F, WPAI, BASDAI, HRU and Derived Endpoints[a])

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
12	2	85	127
24	128	169	Min (211, first dose date from Week 24 dispensed kit)
36	Min (211, first dose date from Week 24 dispensed kit) + 1	253	323
56	324	393	435

a. PASDAS, BASDAI 50 response rates, Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6), ASDAS, proportion of subjects with ASDAS Inactive Disease, proportion of subjects with ASDAS Major Improvement, proportion of subjects with ASDAS Clinically Important Improvement.

b. Day of first dose of study drug.

Table 3. Analysis Windows for Safety Analysis for Period 1 (for Total Cholesterol, HDL-C, LDL-C, Triglycerides, Advanced Lipid Testing[a])

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
4	2	29	57
12	58	85	127
24	128	169	Min (211, first dose date from Week 24 dispensed kit)

a. Advanced lipid testing is exploratory and may not be performed and/or be reported in the CSR.

b. Day of first dose of study drug.

Table 4. Analysis Windows for Efficacy Analysis for Period 1 (for BSA-Psoriasis, PASI, sIGA, LDI, LEI, SPARCC Enthesitis Index and Derived Endpoints[a])

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
12	2	85	99
16	100	113	141
24	142	169	Min (211, first dose date from Week 24 dispensed kit)
36	Min (211, first dose date from Week 24 dispensed kit) + 1	253	323
56	324	393	435

a. MDA, dactylitis count/total enthesitis count, proportion of subjects with resolution of dactylitis/enthesitis (out of all sites, or the sites included in SPARCC or LEI), PAISI75/90/100, 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.

b. Day of first dose of study drug.

Table 5. Analysis Windows for Efficacy Analysis for Period 1 (for SAPS)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
16	2	113	141
24	142	169	Min (211, first dose date from Week 24 dispensed kit)
36	Min (211, first dose date from Week 24 dispensed kit) + 1	253	323
56	324	393	435

a. Day of first dose of study drug.

6.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

6.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics information will be collected at the Baseline visit of the study and will be summarized for the FAS. The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. Categorical or discrete variables will be summarized via frequencies and percentages. Summary statistics will be computed for each treatment group and overall.

Main Demographic and Baseline Characteristics

- Sex (male, female)
- Age (years)
- Age Categories (< 40, [40, 65), ≥ 65 years)
- Race (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Geographic Region (North America, Western Europe and Oceania, Eastern Europe, Latin-America, Asia, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Body Mass Index (BMI) Category (kg/m^2) (BMI < 25, BMI ≥ 25)

PsA Medical History, Prior and Baseline Treatments

- Duration of PsA symptom in years
- Duration of PsA diagnosis in years
- Rheumatoid Factor (RF) status: Positive or Negative
- Anti-CCP status: Positive or Negative

- Number of prior non-biologic DMARDs (0, 1, 2, ≥ 3)
- Number of prior biologic DMARDs (0, 1, 2, ≥ 3)
- Number of prior biologic DMARDs other than anti-TNF (0, 1, 2, ≥ 3)
- Number of prior anti-TNFs (0, 1, 2, ≥ 3)
- Number of prior failed biologic DMARDs (0, 1, 2, ≥ 3)
- Current use of at least 1 non-biologic DMARD at baseline (Yes or No)
- Current NSAID use at baseline (Yes or No)
- Current Corticosteroid use at baseline (Yes or No)
- Concomitant non-biologic DMARD at baseline (MTX alone, MTX and other non-biologic DMARD, non-biologic DMARD other than MTX)

Baseline Disease Characteristics

- Tender joint count (TJC68) defined as the number of tender joints out of 68 assessed joints
- Swollen joint count (SJC66) defined as the number of swollen joints out of 66 assessed joints
- Physician's global assessment of Disease Activity Numeric Rating Scale (0-10 NRS)
- Patient's assessment of pain (0-10 NRS)
- Patient's global assessment of disease activity (0-10 NRS)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- High sensitivity C-reactive protein (hsCRP)
- Categories for hsCRP: equal or below vs. above ULN (2.87 mg/L)
- Body Surface Area (BSA) with Psoriasis (as categorical with < 3%, ≥ 3%)
- Body Surface Area (BSA) with Psoriasis (as continuous for subjects with BSA-Ps > 0%)
- Static Investigator Global Assessment of Psoriasis (sIGA) (as a categorical variable)
- Psoriasis Area and Severity Index (PASI) score (for subjects with ≥ 3% Body Surface Area (BSA) psoriasis)

- Erythrocyte sedimentation rate (ESR)
- Modified Psoriatic Arthritis Response Criteria (PsARC)
- Psoriatic arthritis disease activity score (PASDAS)
- Disease Activity In Psoriatic Arthritis (DAPSA) score
- Presence of Dactylitis
- Leeds Dactylitis Index (LDI) (out of subjects with presence of dactylitis)
- Total dactylitis count (out of subjects with presence of dactylitis)
- Presence of Enthesitis
- Total enthesitis count (out of subjects with presence of enthesitis)
- Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (out of subjects with SPARCC Enthesitis Index > 0)
- Leeds Enthesitis Index (LEI) (out of subjects with LEI > 0)
- DAS28 [CRP]
- DAS28 [ESR]
- Presence of Psoriatic Spondylitis
- Ankylosing Spondylitis Disease Activity Score (ASDAS) (out of subjects with presence of psoriatic spondylitis)
- Bath AS Disease Activity Index (BASDAI) (out of subjects with presence of psoriatic spondylitis)
- Morning stiffness (mean of BASDAI Questions 5 and 6)
- Morning stiffness severity 0-10 (BASDAI Question 5)
- Morning stiffness duration 0-10 (BASDAI Question 6)

Patient Report Outcomes at Baseline

- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- 36-Item Short Form Health Survey (SF-36) Version 2: physical component summary, mental component summary, and the 8 sub-domain scores
- EuroQol-5D-5L (EQ-5D-5L) index and VAS score
- Work Productivity and Activity Impairment (WPAI)
- Self-Assessment of Psoriasis Symptoms (SAPS)

Tobacco/Nicotine and Alcohol Use

- Tobacco/Nicotine Use [user, ex-user, non-user, unknown]
- Alcohol Use [drinker, ex-drinker, non-drinker, unknown]

6.2 Medical History

Medical history data will be summarized and presented for FAS population using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each randomized treatment group as well as overall. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. No statistical comparison will be performed for medical history reporting.

6.3 Prior Treatment and Concomitant Medications

Prior and concomitant medications will be summarized by each randomized treatment group as well as overall for FAS. Prior medications are those medications taken prior to the first dose of study drug. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. Medications taken on the day of the first dose of study drug are not counted as prior medications. Concomitant medications are those medications, other than study drug, taken after the first dose of study drug and within 1 day of the last dose of study drug. This includes medications with a start date between first study drug administration and last study drug administration + 1 day, as well as, medications with a start date prior to first dose of study drug and which are ongoing after first dose of study drug. Medications taken on the day of the first dose of study drug are counted as concomitant medications.

The number and percentage of subjects who received a prior medication and the number and percentage of subjects who received a concomitant medication will be tabulated

separately by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary.

6.4 Protocol Deviations

Protocol deviations based on ICH deviation criteria are categorized as follows:

1. Those who entered the study even though they did not satisfy the entry criteria
2. Those who developed withdrawal criteria during the study and were not withdrawn
3. Those who received the wrong treatment or incorrect dose, and
4. Those who received an excluded or prohibited concomitant medication.

The protocol deviations listed above will be summarized and listed by treatment group.

7.0 Patient Disposition

The following will be summarized by randomized treatment group as well as overall:

- number of subjects randomized,
- number of subjects included in key analysis populations (Full Analysis Set and Per Protocol Analysis Set for efficacy analysis, Safety Analysis Set for safety analysis),
- number of subjects who completed Period 1 study participation,
- number of subjects who entered Period 2,
- number of subjects who completed overall study (Period 1 and Period 2) participation (if applicable).

Premature discontinuation details will be further summarized separately for Period 1 and Period 2 as follows.

Period 1

The number and percentage of subjects who completed Period 1 and prematurely discontinued in Period 1 will be summarized by randomized treatment group, separately by study drug completion/discontinuation and by study participation completion/discontinuation, with the reason for discontinuation collected from the CRF by the following categories:

- Adverse event (AE)
- Withdrew consent
- Lost to follow-up
- Lack of efficacy
- Other.

In addition, the number and percentage of subjects entered Period 2 will be summarized by randomized treatment group.

For Week 24 reporting, this summary will also be presented for study drug completion/discontinuation by Week 24.

Period 2

Period 2 patient dispositions and reason for discontinuation will be summarized with the same categories as given above for Period 1 for overall total and by treatment in Period 2, defined as follows:

1. Upadacitinib 15 mg QD
2. Upadacitinib 30 mg QD

Among the subjects who entered Period 2 participation (regardless of whether subject prematurely discontinued study drug in Period 1), the number and percentage of subjects who completed and prematurely discontinued study participation in Period 2 will be summarized.

Among the subjects who entered Period 2 on study drug, the number and percentage of subjects who completed and prematurely discontinued study drug in Period 2 will be summarized.

8.0 Study Drug Exposure and Compliance

8.1 Study Drug Exposure

The duration of exposure to study drug will be summarized for the safety analysis set by the following groups.

1. Placebo
2. Upadacitinib 15 mg QD

   This includes upadacitinib 15 mg QD exposure from subjects starting on upadacitinib 15 mg QD and subjects switching from placebo to upadacitinib 15 mg QD.
3. Upadacitinib 30 mg QD

   This includes upadacitinib 30 mg QD exposure from subjects starting on upadacitinib 30 mg QD and subjects switching from placebo to upadacitinib 30 mg QD.

Exposure to upadacitinib and placebo is defined as last dose date minus first dose date plus 1 day.

The duration of exposure to study drug will be summarized for each group as specified above, with the number of subjects, mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following cumulative duration intervals.

- ≥ 2 weeks
- ≥ 1 month

- ≥ 3 months
- ≥ 6 months
- ≥ 9 months
- ≥ 12 months
- ≥ 18 months
- ≥ 2 years
- ≥ 2.5 years

8.2 Compliance

Study drug compliance will be summarized for each treatment group at Week 24. The compliance is defined as the number of tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) during the subject's participation up to Week 24 divided by the number of days that the subject was in the Treatment Phase up to Week 24.

9.0 Efficacy Analysis

9.1 General Considerations

There are two sets of planned efficacy analysis: efficacy analysis through Week 24 and long-term efficacy analysis. Unless otherwise noted, all efficacy analyses will be carried out using the FAS population.

9.1.1 Efficacy Analysis at Different Phases of the Study

Efficacy Analysis Through Week 24

Efficacy analysis by randomized treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD and the combined placebo group) will be performed on efficacy data up to Week 24. No protocol-defined treatment switching will occur prior to the time point. Formal statistical inference will be generated, and results from this set of analysis will be used as the key efficacy findings of this study.

Long-Term Efficacy Analysis

Long-term efficacy analysis will be performed on As Observed data (defined in Section 9.1.2) by randomized treatment group sequence as described below:

1. Placebo → Upadacitinib 15 mg QD
2. Placebo → Upadacitinib 30 mg QD
3. Upadacitinib 15 mg QD
4. Upadacitinib 30 mg QD

Descriptive statistics and 95% confidence intervals will be provided for all treatment sequences.

9.1.2 Definition of Missing Data Imputation

Non-Responder Imputation (NRI) Approach

The NRI approach will categorize any subject who has a missing value for categorical variables at a specific visit as non-responder for that visit. In addition, subjects who prematurely discontinue from study drug will be considered as non-responders for all subsequent visits after discontinuation.

As Observed (AO)

The AO 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 AO analysis for that visit. All observed data will be used in the analysis regardless of treatment adherence or rescue.

Mixed-Effects Model Repeated Measures (MMRM)

The repeated measure analysis will be conducted using mixed models including observed data at all visits. Data collected after premature discontinuation of study drug will be excluded from the analysis. The mixed model includes the categorical fixed effects of

treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) and the continuous fixed covariates of baseline measurement. An unstructured variance covariance matrix will be used. The parameter estimations are based on the assumption of data being missing at random (MAR) and using the method of restricted maximum likelihood (REML).

The NRI approach will serve as the primary analysis approach for binary endpoints, while As Observed (AO) analysis will be repeated as a sensitivity analysis. The MMRM will serve as the primary analysis for continuous 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 additional sensitivity analysis for selected key endpoints to account for potential deviation from the MAR assumption.

9.2 Efficacy Analysis Through Week 24

9.2.1 Primary Efficacy Analysis of Primary Efficacy Endpoint

The primary endpoint is ACR20 response at Week 12. Analysis of the primary endpoint will be conducted on the FAS based on randomized treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD versus the combined placebo group). Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Comparisons of the primary endpoint will be made between each upadacitinib dose and the combined placebo group using the Cochran-Mantel-Haenszel test (refer to Appendix A) adjusting for the main stratification factor of current DMARD use (yes/no). Point estimate, 95% CI using normal approximation and p-value for the treatment difference will be presented. Both the nominal p-value constructed using the Cochran-Mantel-Haenszel test and the adjusted p-value through the graphical multiplicity procedure described in Section 9.2.5 will be provided. For the primary analysis, non-responder imputation (NRI) will be used.

9.2.2 Sensitivity Analysis of Primary Efficacy Endpoint

The primary analysis will be repeated using As Observed (AO) data without any imputation as a sensitivity analysis. This will be conducted on the FAS based on randomized treatment groups.

Supportive NRI analysis will also be conducted on the Per Protocol Analysis Set.

9.2.3 Key Secondary Efficacy Analyses

The following is a list of ranked key secondary endpoints:

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 (for subjects with baseline sIGA ≥ 2);
3. Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with $\geq 3\%$ BSA psoriasis at baseline);
4. Change from baseline in SF-36 PCS at Week 12;
5. Proportion of subjects achieving Minimal Disease Activity (MDA) at Week 24;
6. Change from baseline in FACIT-Fatigue at Week 12;
7. Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS) at Week 16.

Additional key secondary efficacy endpoints are:

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

For binary endpoints, frequencies and percentages will be reported for each treatment group. NRI will be used as primary analysis. For MDA at Week 24, subjects who meet the rescue criteria (i.e., 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 be treated as non-responders. AO will be used as sensitivity analysis. Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Treatment comparisons will be made between each upadacitinib dose and the combined placebo group using the Cochran-Mantel-Haenszel test (refer to Appendix A) adjusting for the main stratification factor of current DMARD use (yes/no). Point estimate, 95% CI using normal approximation and the p-value for the treatment difference will be presented. For the primary NRI analysis, both the nominal p-value and the adjusted p-value through the graphical multiplicity procedure described in Section 9.2.5 will be provided.

For continuous endpoints, the LS mean and 95% CI for each randomized treatment group and the LS mean treatment difference, the associated 95% CI and the p-value between each upadacitinib dose group and the combined placebo group will be provided using the MMRM model as described in Section 9.1.2, with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no) and the continuous fixed covariates of baseline measurement. Both the nominal p-value and the adjusted p-value through the graphical multiplicity procedure described in Section 9.2.5 will be provided.

9.2.4 Efficacy Analyses for Additional Secondary Endpoints

Additional efficacy analysis includes the following endpoints at the scheduled time points other than those specified for the primary and key secondary variables:

- 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) (for subjects with baseline presence of dactylitis);
- Change from baseline in dactylitis count (for subjects with baseline presence of dactylitis);
- Proportion of subjects with resolution of dactylitis (for subjects with baseline presence of dactylitis);
- Change from baseline in LEI (for subjects with baseline LEI > 0);
- Proportion of subjects with resolution of enthesitis sites included in the LEI (for subjects with baseline LEI > 0);
- Change from baseline in SPARCC Enthesitis Index (for subjects with baseline SPARCC Enthesitis Index > 0);
- Proportion of subjects with resolution of enthesitis sites included in the SPARCC Enthesitis Index (for subjects with baseline SPARCC Enthesitis Index > 0);
- Change from baseline in total enthesitis count (for subjects with baseline total enthesitis count > 0);
- Proportion of subjects with resolution of enthesitis (for subjects with baseline total enthesitis count > 0);
- 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 (for subjects with baseline sIGA ≥ 2);

- Change from baseline in BSA-Ps (for subjects with baseline BSA > 0%);
- Change from baseline in Modified Psoriatic Arthritis Response Criteria (PsARC);
- 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;
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue;
- Change from baseline in EuroQol-5D-5L (EQ-5D-5L) index and VAS score;
- Change from baseline in Work Productivity and Activity Impairment (WPAI);
- Cumulative Health Resource Utilization (HRU);
- Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS);
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (out of subjects with presence of psoriatic spondylitis at baseline);
- BASDAI 50 response rates (out of subjects with presence of psoriatic spondylitis at baseline);
- Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6)
- Change from baseline in Morning stiffness severity 0-10 (BASDAI Question 5)
- Change from baseline in Morning stiffness duration 0-10 (BASDAI Question 6)
- Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects with ASDAS Inactive Disease (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects with ASDAS Major Improvement (out of subjects with presence of psoriatic spondylitis at baseline);

- Proportion of subjects with ASDAS Clinically Important Improvement (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35).

For binary endpoints, frequencies and percentages will be reported for each treatment group. NRI will be used as primary analysis. In addition, subjects who meet the rescue criteria (i.e., 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 be treated as non-responders at subsequent visits. AO will be used as sensitivity analysis. Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Treatment comparisons will be made between each upadacitinib dose and the combined placebo group using the Cochran-Mantel-Haenszel (refer to Appendix A) test adjusting for the main stratification factor of current DMARD use (yes/no). Point estimate, 95% CI using normal approximation and the nominal p-value for the treatment difference will be presented.

For continuous endpoints, the LS mean and 95% CI for each randomized treatment group and the LS mean treatment difference, the associated 95% CI and the p-value between each upadacitinib dose group and the combined placebo group will be provided using MMRM model as described in Section 9.1.2, with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no) and the continuous fixed covariates of baseline measurement. The nominal p-value will be provided.

9.2.5 Handling of Multiplicity

The overall type I error rate of the primary and ranked key secondary endpoints for the two doses will be strongly controlled using a graphical multiple testing procedure.[1] Specifically, the testing will utilize the endpoint sequence of primary endpoint followed by the ranked key secondary endpoints in the order as specified in Section 9.2.3, and will begin with testing the primary endpoint using α of 0.025 for each dose. Continued testing

will follow a pre-specified α transfer path which includes downstream transfer along the endpoint sequence within each dose as well as cross-dose transfer. Adjusted p-values for the primary and ranked key secondary endpoints will be provided based on the testing procedure.

The graph for the testing procedures is provided in Figure 2. In the graph, the arrows specify the α transfer paths. Once an endpoint is rejected (i.e., deemed significant) at its assigned significance level, its significance level will be transferred to subsequent endpoint(s) following the arrow(s). The numbers on the arrows denote the weights for transferring significance levels. Specifically, the weight 1 denotes 100% transfer of significance level.

In addition, within each dose the last two ranked key secondary endpoints (FACIT and SAPS), will be tested together using Hochberg procedure.[2] The significance level assigned to this group of endpoints will continue to be transferred if both endpoints in the group are rejected by the Hochberg procedure at the given significance level.


CCI

9.2.6 Efficacy Subgroup Analysis

The primary efficacy endpoint will be examined in the subgroups listed in Table below. Treatment difference between each upadacitinib dose and the combined placebo group will be presented with point estimate and 95% confidence interval using normal approximation. No p-value will be provided for subgroup analysis. If any of the resulting subgroups for a variable has fewer than 10% of the planned study size (i.e., < 63 subjects), the subgroup may be collapsed into the next subgroup with a larger sample size.

Table 6. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	< 40, [40, 65), ≥ 65
Sex	Male or Female
BMI	< 25 kg/m^2 or ≥ 25 kg/m^2
Race	White, Non-white
Geographic region	North America, Western Europe and Oceania, Eastern Europe, Latin-America, Asia, and Other
Duration of PsA diagnosis	≤ 5, (5, 10], > 10 years
Baseline hsCRP	≤ ULN or > ULN
Number of prior failed biologic DMARDs	= 1, > 1
Current use of non-biologic DMARDs	Yes or No

9.3 Long-Term Efficacy Analysis

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 56 and every 12 weeks thereafter until completion of the study:

- ACR20/50/70 response rates
- Change from baseline in individual ACR components
- Change from baseline in DAS28 (CRP) and DAS28 (ESR)
- Change from baseline in PsARC
- Change from baseline in DAPSA

- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35)

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 12, 24, 36, 56 and every 12 weeks thereafter until completion of the study:

- Change from baseline in EQ-5D-5L index and VAS score
- Change from baseline in FACIT-F
- Change from baseline in SF-36
- Change from baseline in WPAI
- Change from baseline in BASDAI
- Cumulative HRU
- Change from baseline in PASDAS
- BASDAI 50 response rates
- Change from baseline in ASDAS
- Proportion of subjects with ASDAS Inactive Disease
- proportion of subjects with ASDAS Major Improvement
- proportion of subjects with ASDAS Clinically Important Improvement

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 12, 16, 24, 36, 56 and every 12 weeks thereafter until completion of the study:

- Change from baseline in BSA-Ps
- PASI 75/90/100 response rates
- Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline
- Proportion of subjects achieving Minimal Disease Activity (MDA)
- Change from baseline in LDI
- Change from baseline in LEI
- Change from baseline in SPARCC enthesitis index
- Change from baseline in dactylitis count

- Proportion of subjects with resolution of dactylitis
- Proportion of subjects with resolution of enthesitis sites included in the LEI
- 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

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 16, 24, 36, 56 and every 12 weeks thereafter until completion of the study:

- Change from baseline in SAPS

Descriptive statistics will be provided for each randomized treatment group sequence as defined in Section 9.1.1. These include the number of observations, mean, standard deviation, 95% CI, median, minimum, Q1, Q3 and maximum for continuous endpoints; and frequencies and percentages with 95% CI using normal approximation for binary endpoints. Plot for each randomized treatment group sequence over time will be provided for key endpoints. These efficacy analyses will be based on As Observed (AO) analysis.

9.4 Efficacy Variables Definitions and Conventions

9.4.1 ACR Criteria

ACR criteria are a commonly used standard criteria set mentioned in the FDA industry guidance to evaluate the effectiveness of investigational drug in reduction of disease activity. It is a composite measurement calculated based on the improvement over a set of core measurements.

ACR20 is defined as at least 20% improvement (compared to baseline values) in tender and swollen joint counts and at least 20% improvement in 3 of the remaining 5 core set measures (subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant hsCRP).

ACR50 and ACR70 are similarly defined with at least 50% and 70% improvement, respectively.

A subject will be classified as an ACR20 (ACR50, ACR70) responder, if the following conditions are met:

1. ≥ 20% (50%, 70%) improvement from baseline in tender joint count (TJC68) and
2. ≥ 20% (50%, 70%) improvement from baseline in swollen joint count (SJC66) and
3. ≥ 20% (50%, 70%) improvement from baseline in at least 3 of the following 5:
    - patient's assessment of pain
    - patient's global assessment of disease activity (PtGA)
    - physician's global assessment of disease activity (PGA)
    - patient's self-assessment of physical function (i.e., measured by Health Assessment Questionnaire HAQ-DI score)
    - Acute-phase reactant value high-sensitivity CRP (hsCRP)

Seven components are included in the ACR response criteria. Missing values for a component can occur due to data collection issues for a particular form, a missed visit or dropout from the study. Depending on the pattern of the missing components, ACR responses may be or may not be determined for a visit date using (partially) observed values only. In the case when ACR responses cannot be determined for any visit date within a visit window, partially observed data from different visit dates within the same visit window can be combined to determine ACR responses for the visit window.

To maximize the utilization of observed information at certain visits and be scientifically as robust as possible, the principle to calculate ACR response is to minimize imputation whenever possible. "As Observed" ACR response will be calculated first based on a derived visit window instead of the nominal visit identifier (e.g., Week 6 visit) collected from the CRF.

To calculate "as observed" ACR responses:

Identify the observed component 20% improvement indicator (0/1/missing), 1 means achieving ≥ 20% improvement from baseline and 0 means < 20% improvement from baseline.

ACR20 = 0 if TJC indicator = 0 OR SJC indicator = 0 OR at least 3 out of 5 components improvement indicators = 0;

ACR20 = 1 if TJC indicator = 1 AND SJC indicator = 1 AND at least 3 out of 5 components improvement indicators = 1

For all other cases, "as observed" ACR20 = missing since ACR20 cannot be determined.

The following table illustrates examples for observed ACR calculations.

Example	TJC 68	SJC 66	Component 1	Component 2	Component 3	Component 4	Component 5	ACR20-Response?
A	1	1	1	1	1	.	.	Yes
B	1	0	1	1	1	1	1	No
C	.	0	.	.	.	.	.	No
D	1	.	1	1	1	1	1	.
E	1	1	0	0	0	1	1	No
F	.	.	0	0	0	.	.	No
G	1	1	1	1	0	0	.	.

Legend: 1 = ≥ 20% improved compared to baseline; 0 = < 20% improved compared to baseline; "." Missing

Derived visit windowing Rule for ACR Response Calculation:

To identify the component value in a visit window:

ACR component values will first be determined at each date within a visit window.

ACR component values at each date will be combined to determine the "as observed" ACR composite score at each date in each window.

After this calculation, if multiple non-missing ACR composite scores are available within a given visit window, the non-missing ACR composite score closest to the target day will be used. If two composite scores have the same distance from the target day, the later one will be used. The corresponding date will be used as the "as observed" ACR response date in the derived efficacy dataset.

If a non-missing ACR composite score is not available for any day within a given visit window, the windowed component values for that visit will be used to calculate the ACR composite score for that visit window (component value windowing follow the same rules as in steps described above). Date of TJC will be used as the "as observed" ACR date in the derived efficacy dataset.

The following rules are applied for the NRI imputation for the ACR responses.

Non-Responder Imputation (NRI):

- Step 1: all missing components will be imputed using LOCF, and then the ACR composite score can be calculated
- Step 2: if the ACR composite score cannot be determined by step 1, the ACR composite score will be imputed as 0. In addition, subjects who prematurely discontinue from the study drug will be considered as non-responders (ACR = 0) for all subsequent visits after the discontinuation date.

9.4.2 Joint Evaluation

Anatomical joints are evaluated for swelling and tenderness at every study visit. The 34 anatomical joints in Table 7 are assessed in this study for both the left and right side of the body.

Table 7. Anatomical Joints Assessed for Calculation of Tender and Swollen Joint Counts (TJC68 and SJC66)

Temporomandibular	Sternoclavicular	Acromio-clavicular	Shoulder
Elbow	Wrist	Metacarpophalangeal I	Metacarpophalangeal II
Metacarpophalangeal III	Metacarpophalangeal IV	Metacarpophalangeal V	Thumb Interphalangeal
Proximal Interphalangeal II	Proximal Interphalangeal III	Proximal Interphalangeal IV	Proximal Interphalangeal V
Distal Interphalangeal II	Distal Interphalangeal III	Distal Interphalangeal IV	Distal Interphalangeal V
Hip[a]	Knee	Ankle	Tarsus
Metatarsophalangeal I	Metatarsophalangeal II	Metatarsophalangeal III	Metatarsophalangeal IV
Metatarsophalangeal V	Great Toe/Hallux	Interphalangeal II	Interphalangeal III
Interphalangeal IV	Interphalangeal V		

a. Hip joints are not assessed for swelling.

At each study visit, a joint evaluator will assess whether a particular joint was "tender or painful" where presence of tenderness is scored as "1" and the absence of tenderness is scored as "0," provided the joint was not replaced ("9") or could not be assessed ("NA") due to other reasons (e.g., post-corticosteroid joint injection). The total tender joint count (TJC68), which is based on 68 joints, will be derived as the sum of all "1s" and proportional extrapolation will be used to impute joint counts for the joints that are replaced or not assessed. A similar method will be followed for the derivation of total swollen joint count (SJC66), which is based on 66 joints as the hip joints are excluded. Thus, the range for TJC68 will be 0 to 68 and 0 to 66 for SJC66.

9.4.3 Patient's Global Assessment of Disease Activity Numeric Rating Scale (NRS)

The subject will assess his/her disease activity using the Patient's Global Assessment of Disease NRS. The range is 0 to 10 with no activity being indicated by 0 and severe activity by 10.

9.4.4 Physician's Global Assessment of Disease Activity Numeric Rating Scale (NRS)

The physician will assess Patient's disease activity at the time of visit using the Physician's Global Assessment of Disease NRS. The range is 0 to 10 with no activity being indicated by 0 and severe activity by 10.

9.4.5 Patient's Assessment of Pain Numeric Rating Sale (NRS)

The subject will assess his/her pain using the Patient's Global Assessment Pain NRS. The range is 0 to 10 with no activity being indicated by 0 and severe activity by 10.

9.4.6 Disease Activity Score (DAS28)

DAS28 (CRP) and DAS28 (ESR) are composite indices to assess disease activity in PsA using hsCRP or ESR measurement, respectively. The DAS28 provides a score between 0 and 10, indicating arthritis disease activity at the time of measurement.

DAS28 (CRP) and DAS28 (ESR) is calculated based on Tender Joint Count, Swollen Joint Count, PtGA of Disease Activity (0-100), and hsCRP (in mg/L) or ESR (mm/hr).

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

$$\text{DAS28 (ESR)} = 0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \ln(\text{ESR}^{\#}) + 0.014 \times \text{PtGA}^{\gg}$$

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

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

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

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

\# ESR refers to the Erythrocyte sedimentation rate. ESR unit in the DAS28 (ESR) equation is expressed as mm/hr.

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

Table 8. Anatomical Joints for DAS28 (CRP) Calculation

Shoulder	Elbow	Wrist	Thumb Interphalangeal
Metacarpophalangeal I	Metacarpophalangeal II	Metacarpophalangeal III	Metacarpophalangeal IV
Metacarpophalangeal V	Proximal Interphalangeal II	Proximal Interphalangeal III	Proximal Interphalangeal IV
Proximal Interphalangeal V	Knee		

As PtGA of Disease Activity is collected with the scale of 0-10 NRS, the variable needs to be multiplied by 10 before being used the DAS28 formula.

To calculate observed DAS28 scores, the observed component value will be calculated first. Then the components will be included in the calculation per the DAS formula selected. If any observed component is missing in a window, then the observed DAS28 score will be missing.

9.4.7 Disease Activity in Psoriatic Arthritis (DAPSA) Score

DAPSA is a continuous endpoint that measures the disease activity in psoriatic arthritis. DAPSA consists of five components: Tender Joint Count 68, Swollen Joint Count 66, Patient's Assessment of Pain (0-10 NRS), PtGA of Disease Activity (0-10 NRS), and hsCRP (in mg/dL).

DAPSA = SJC66 + TJC68 + Pt pain (0-10 NRS) + PtGA (0-10 NRS) + hsCRP (in mg/dL)

To calculate observed DAPSA scores, the observed component value will be calculated first. Then the components will be included in the calculation per the DAPSA formula. If any observed component is missing in a window, then the observed DAPSA score will be missing.

9.4.8 PsA Disease Activity Score (PASDAS)

PASDAS is a continuous scale of combined joint, dactylitis and enthesitis assessments, physician and patient global assessments for arthritis, SF36-PCS, and hsCRP measurements.

PASDAS = (((0.18 $\sqrt{}$ (PGA)) + 0.159 $\sqrt{}$ (PtGA) - 0.253 $\sqrt{}$ (SF36-PCS) + 0.101 ln (SJC66 + 1) + 0.048 ln (TJC68 + 1) + 0.23 ln (Leeds Enthesitis Index+ 1) + 0.37 ln (Tender Dactylitis Count + 1) + 0.102 ln (hsCRP + 1) + 2) * 1.5,

where $\sqrt{}$ is square root and ln is natural log. PtGA is on the scale of 0 – 100 and PGA is on the scale of 0 – 100. As PtGA and PGA are collected with the scale of 0-10 NRS, their values need to be multiplied by 10 before being used in the PASDAS formula.

SF36-PCS is the physical component scale in SF36 instrument. The unit for hsCRP is mg/L.

The tender dactylitis count is based on the dactylitis assessment. The count is calculated by summing the digits with a "presence of tenderness" score = 1.

The Leeds Enthesitis Index (LEI) evaluates enthesitis at 6 most commonly involved entheseal sites, as indicated in the table below. The LEI is calculated by taking the sum of the scores from the 6 sites. The LEI ranges from 0 to 6.

		Tenderness in Left			Tenderness in Right		
		YES = 1	NO = 0	Not Assessed = NA	YES = 1	NO = 0	Not Assessed = NA
1	Lateral epicondyle						
2	Achilles tendon insertion						
3	Medial femoral condyle						

To calculate observed PASDAS scores, the observed component value will be calculated first. Then the components will be included in the calculation per the PASDAS formula. If any observed component is missing in a window, then the observed PASDAS score will be missing.

9.4.9 Disability Index of Health Assessment Questionnaire (HAQ-DI)

HAQ-DI is a self-reported patient outcome measurement. It is calculated as the mean of the scores from 8 following categories with a range 0 – 3: Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. Higher scores reflect greater disability.

The maximum score for all the questions in each category is considered as the score for the category. The HAQ-DI takes into account the subject's use of aids or devices or assistance in the scoring algorithm for a disability category. For each category there is an AIDS OR DEVICES companion variable that is used to record the type of assistance, if any, a subject uses for his/her usual activities. If aids or devices and/or assistance from another person are checked for a category, the score for this category is set to 2 (much difficulty), if the original score is 0 (no difficulty) or 1 (some difficulty). The HAQ-DI is then calculated by summing the adjusted categories scores and dividing by the number of categories answered. The HAQ-DI cannot be calculated if the subject does not have scores for at least 6 categories.

9.4.10 Static Investigator Global Assessment of Psoriasis (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 assessment, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit. A lower score indicates less severe psoriasis (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe).

A binary clinical endpoint based on sIGA is considered in this study. It is the proportion of subjects achieving a sIGA score of 0 or 1 and at least a 2-point improvement from baseline. This endpoint is calculated among the subjects with baseline sIGA score ≥ 2.

9.4.11 Psoriasis Area Severity Index (PASI)

Psoriasis Area Severity Index (PASI) has four anatomic sites – head, upper extremities, trunk, and lower extremities – which are assessed for erythema, induration and desquamation using a 5-point scale:

- 0 = no symptoms
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

Based on the extent of lesions in a given anatomic site, the area affected is assigned a numerical value:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% – 29%
- 3 = 30% – 49%
- 4 = 50% – 69%
- 5 = 70% – 89%
- 6 = 90% – 100%

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:

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

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.

If an item is missing, PASI is not scored.

PASI 75 (PASI 50, PASI 90, PASI 100) response is achieved if there is at least a 75% (50%, 90%, 100%) reduction in PASI score (≥ PASI 75/50/90/100 response) at a visit relative to the Baseline PASI score.

PASI is summarized in subjects with ≥ 3% BSA (Body Surface Area) psoriasis involvement at baseline.

9.4.12 Minimum Disease Activity for PsA

A patient is classified as in MDA when 5 of the following 7 criteria are met:

- TJC68 ≤ 1
- SJC66 ≤ 1
- PASI ≤ 1 or BSA-Ps ≤ 3%
- Patient's assessment of pain ≤ 1.5 (0-10 NRS)
- Patient's Global Assessment of disease activity ≤ 2 (0-10 NRS)
- HAQ-DI score ≤ 0.5
- Leeds Enthesitis Index ≤ 1

MDA response can be determined if at least 5 of the 7 criteria are met (responder), or if at least 3 of the 7 criteria are not met (non-responder). Selection of multiple MDA responses within one visit window follows the same rules as ACR. Missing values for each component can occur due to data collection issues for a particular form, a missed visit or dropout from the study. Depending on the pattern of the missing components, MDA responses may be or may not be determined for a visit date using (partially) observed values only. In the case when MDA responses cannot be determined for any

visit date within a visit window, partially observed data from different visit dates within the visit window can be combined to determine MDA responses for the visit window.

9.4.13 Self-Assessment of Psoriasis Symptoms (SAPS)

The Self-Assessment of Psoriasis Symptoms (SAPS) contains 11 symptom-focused items. Each item is scored from 0 to 10, with 0 being least severe and 10 being most severe. The total score is generated by summing the 11 items. The total score ranges from 0 to 110.

9.4.14 Leeds Dactylitis Index (LDI) and Dactylitis Count

The Leeds Dactylitis Index (LDI) is a score based on finger circumference and tenderness, assessed and summed across all dactylitic digits. The presence of dactylitis digit is defined as at least one affected AND tender digit with circumference increase over reference digit ≥ 10%. For each of 20 digits of a subject, a digit final score needs to be calculated first. For an unaffected digit, the digit final score is set to be 0. For an affected digit, the digit final score is calculated as (A/B-1)*100*C if A/B ≥ 1.1, and digit finals score = 0 if A/B < 1.1, where A denotes the circumference of the digit, B the reference circumference, and C the tenderness score. The reference circumference can be either the circumference of the unaffected contralateral digit if available, or from a reference table if otherwise. LDI is the sum of the digit final scores over all 20 digits.

The dactylitis count will be calculated as the number of digits (hands and feet) with presence of dactylitis. The count ranges from 0 to 20.

The proportion of subjects with resolution of dactylitis is defined as the proportion of subjects with LDI = 0.

9.4.15 Leeds and SPARCC Enthesitis Indices and Total Enthesitis Count

For the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index 16 sites are evaluated as indicated in rows 1 – 8 in the table below. Tenderness on examination is recorded as either present (coded as 1), absent (coded as 0), or not assessed

for each site. The SPARCC enthesitis index is calculated by taking the sum of the scores from the 16 sites. The SPARCC score ranges from 0 to 16.

The Leeds Enthesitis Index evaluates enthesitis at the 6 entheseal sites indicated in rows 2, 7 and 9 in the table below. Tenderness on examination is recorded as either present (coded as 1), absent (coded as 0), or not assessed for each of the 6 sites. The LEI is calculated by taking the sum of the scores from the 6 sites. The LEI ranges from 0 to 6.

The total enthesitis count is calculated by taking the sum of the tenderness scores from all 18 sites in the table below.

The proportion of subjects with resolution of enthesitis sites included in the LEI is defined as the proportion of subjects with LEI = 0; the proportion with resolution of the SPARCC Enthesitis Index and of the total enthesitis count are similarly defined.

		Tenderness in Left			Tenderness in Right		
		Present = 1	Absent = 0	Not Assessed = NA	Present = 1	Absent = 0	Not Assessed = NA
1	Medial epicondyle						
2	Lateral epicondyle						
3	Supraspinatus insertion into the greater tuberosity of humerus						
4	Greater trochanter						
5	Quadriceps insertion into superior border of patella						
6	Patellar ligament insertion into inferior pole of patella or tibial tubercle						
7	Achilles tendon insertion into calcaneum						
8	Plantar fascia insertion into calcaneum						
9	Medial femoral condyle						

9.4.16 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 by the physician is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved.

9.4.17 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Morning Stiffness Score

The BASDAI is composed of 6 items investigating 5 domains (fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness), with 1 item for each of the first four domains and 2 items for the last domain (morning stiffness). Each item is scored on a 0-10 NRS. A lower score indicates less disease activity.

Scoring of the BASDAI is as follows:

1. Measure each item of the BASDAI in NRS (out of a total of 10)
2. BASDAI Score = 0.2*(Item1 + Item2 + Item3 + Item4 + 0.5*Item5 + 0.5* Item6)

The BASDAI Score ranges from 0 – 10. If one of the 5 items (Questions 1 – Question 4, inflammation) is missing, then the score is the mean of the 4 non-missing items (total of 4 non-missing items divided by 4). If more than 1 of the 5 items is missing, then the BASDAI score is missing.

Note: Question 5 and Question 6 jointly constitute Item 5 (inflammation). If both Questions 5 and 6 are missing, and questions 1 through 4 are non-missing, then only one item will be considered missing. The BASDAI score can still be calculated as the mean of Questions 1 – 4. However, if, for example, both Question 6 and Question 1 are missing, then 2 items will be considered missing, as the inflammation calculation would be incomplete. The BASDAI score would then be considered missing in this case.

The Morning Stiffness Score is the average of BASDAI questions 5 and 6 and it ranges from 0 – 10.

9.4.18 Modified Psoriatic Arthritis Response Criteria (PsARC)

The modified PsARC is a PsA-specific composite responder index. To achieve response, a subject must achieve 2 of the following 4 items, one of which has to be a Tender Joint Count 68 or Swollen Joint Count 66, and no worsening of any measure:

- ≥ 30% improvement in TJC68
- ≥ 30% improvement in SJC66
- Improvement in PtGA of Disease Activity NRS
- Improvement in PGA of Disease Activity NRS

Four components are included in the PsARC criteria. Missing values for each component can occur due to data collection issues for a particular form, a missed visit or dropout from the study. In the case when PsARC responses cannot be determined for any visit date within a visit window, partially observed data from different visit dates within the visit window can be combined to determine PsARC responses for the visit window.

9.4.19 Ankylosing Spondylitis Disease Activity Score (ASDAS)

Parameters used for the calculation of ASDAS:

1. Patient's assessment of total back pain (BASDAI Question 2)
2. PtGA of disease activity (0-10 NRS)
3. Peripheral pain/swelling (BASDAI Question 3)
4. Duration of morning stiffness (BASDAI Question 6)
5. High-sensitivity C-reactive protein (hs-CRP) in mg/L.

Calculation of ASDAS:

$ASDAS_{hs\text{-}CRP}$ = 0.121 × total back pain + 0.110 × PtGA + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(hs-CRP+1).

To calculate observed ASDAS scores, the observed component value will be calculated first. Then the components will be included in the calculation per the ASDAS formula. If any observed component is missing in a window, then the observed ASDAS score will be missing.

ASDAS score is categorized by the following ASDAS Disease Activity States:

- ASDAS Inactive Disease: ASDAS < 1.3
- ASDAS Moderate Disease: 1.3 ≤ ASDAS < 2.1
- ASDAS High Disease: 2.1 ≤ ASDAS ≤ 3.5
- ASDAS Very High Disease: ASDAS > 3.5

ASDAS Response categories are defined as follows:

- ASDAS Major Improvement (a change from baseline ≤ –2.000)
- ASDAS Clinically Important Improvement (a change from baseline ≤ –1.100)

9.4.20 FACIT-Fatigue Questionnaire (FACIT-F)

The FACIT Fatigue Questionnaire is a 13-item tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point scale (4 = not at all fatigued to 0 = very much fatigued). The Fatigue scale ranges from 0 to 52, with higher scores indicating less fatigue.

Item score for each item is calculated by either subtracting from 4 or adding 0 depending on whether it is a reversal item or not. FACIT Fatigue Scale is then calculated by adding up all item scores, multiplying by 13 and dividing by the number of items answered. If less than 7 items are answered, the scale will not be computed.

9.4.21 EuroQoL-5D (EQ-5D-5L)

EQ-5D measures 5 dimensions of health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels per dimension (no problems, slight problems, moderate problems, severe problems, and extreme problems corresponding to Level 1 to Level 5 respectively) and includes the EQ Visual Analogue Scale (EQ VAS). The 5 dimensions of health status are converted into a single index value. The change from baseline of the index value and the EQ VAS will be analyzed and reported. UK scoring algorithm will be used.

9.4.22 Form SF-36v2

The 36-Item Short Form, Version 2 (SF-36v2) health survey consists of 36 general health questions. It has 2 components: physical and mental. For each component, a transformed summary score is calculated using 8 sub domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

The coding and scoring for the SF-36 will use the software provided by QualityMetrics.

9.4.23 Work Productivity and Activity Impairment Questionnaire Psoriatic Arthritis (WPAI-PsA)

The Work Productivity and Activity Impairment Questionnaire: Psoriatic Arthritis, V2.0 (WPAI-PsA) was developed to measure the effect of overall health and specific symptoms on productivity at work and outside of work. It consists of 6 questions. A lower WPAI-PsA score indicates an improvement. The WPAI PsA is collected at the designated study visits listed in the protocol. The WPAI-PsA coding and scoring methods are described in the following:

The 6 measures will be derived based on the responses from the 6 questions. The 4 main impairment scores (S1 to S4) are expressed as *percent impairment* based on the 6 questions.

Scores:

S0. Employment: defined below in missing data handling conventions

S1. Absenteeism: Percent work time missed due to PsA:

$$100 \times \left[\frac{Q2}{Q2 + Q4} \right]$$

S2. Presenteeism: Percent impairment while working due to PsA:

$$100\times\left[\frac{Q5}{10}\right]$$

S3. Percent overall work impairment due to PsA:

$$100\times\left[\frac{Q2}{Q2+Q4}+\left\{1-\frac{Q2}{Q2+Q4}\right\}\times\frac{Q5}{10}\right]$$

S4. Percent activity impairment due to PsA:

$$100\times\left[\frac{Q6}{10}\right]$$

S5. Did subject miss work (defined below). This is needed to derive the proportion of subjects who missed work.

Missing Data Handling Conventions

When calculating the WPAI: PsA scores, the following computational notes should be followed.

- Define Employment as a binary YES or NO variable where YES corresponds to "Employed" and NO corresponds to "Not Employed."
  - A subject will be considered "employed" at a given visit if Q1 = YES or Q2 > 0 or Q4 > 0.
  - A subject will be considered "unemployed" at a given visit if Q1 = NO and no positive hours recorded under Q2 and Q4 (i.e., if Q1 = NO AND Q2 ≤ 0 AND Q4 ≤ 0, then UNEMPLOYED).
  - Employment status for a subject will be considered "missing" at a given visit if Q1 = missing and no positive hours recorded under Q2 and Q4.

- If a subject is "unemployed" or employment status is "missing," then S1, S2, and S3 will be set to "missing."
- If Q2 = 0 and Q4 = 0 or missing then Q2/(Q2 + Q4) = missing (i.e., S1 = missing).
- If Q2 = 0 and Q4 = 0, then set S3 to missing.
- If Q2 is missing or Q4 is missing, then set S1 and S3 to missing.
- If Q4 = missing, then DO NOT set Q5 = missing.
- If Q5 is missing, then apply the following rules:
  - If Q2 > 0, Q4 = 0, and Q5 = missing, then S3 = 100%.
  - If Q2 = 0, Q4 > 0, and Q5 = missing, then S3 is missing.
  - If Q2 > 0, Q4 > 0, and Q5 = missing, then S3 is missing.
- Determine if a subject missed work (based on Q2) in order to analyze the proportion of subjects who missed work:
  - Create a binary (yes or no) "missed work" variable.
  - A subject will be considered as yes to missed work if Q2 is greater than 0.
  - If Q2 = missing, then MISSED WORK = missing.
  - If Q2 > 0, then MISSED WORK = "yes."
  - If Q2 = 0, then MISSED WORK = "no."

Therefore, the proportion of subjects who missed work will be counted based on the number of subjects with MISSED WORK = YES.

9.4.24 Health Resource Utilization (HRU) Questionnaire

The HRU questionnaire contains three questions regarding health care utilization in the following categories: unscheduled health care professional visits, emergency room visits, and hospital admissions. The data gathered from the HRU questionnaire will be used to calculate the individual cumulative number of utilizations per time (e.g., subject-year) under observation in each category (i.e., unscheduled PsA-related health care professional visits, emergency room visits, hospital admissions and the total number of days in hospital) as follows:

- Time under observation for a subject will be defined as "date of last visit with non-missing HRU – date of baseline visit."
- The number of utilizations after baseline will be summed up for each subject.

To determine cumulative HRU over all subjects, the ratio of the total number of utilizations (i.e., over all subjects) and the total time under observation (i.e., over all subjects) will be calculated across all subjects in each treatment group. HRU will be analyzed as observed only.

10.0 Safety Analysis

10.1 General Considerations

Safety analyses will be carried out using the Safety Analysis Set by "as treated" treatment groups. There are two sets of planned safety analysis: safety analysis through Week 24, and long-term safety analysis.

Safety Analysis Through Week 24

Standard safety analyses by the "as treated" treatment groups of upadacitinib 15 mg QD, upadacitinib 30 mg QD, and the combined placebo group will be performed on safety data up to Week 24. No protocol-defined treatment switching will occur prior to this time point.

The standard safety analyses will include reporting of adverse events (AEs), laboratory, and vital signs measurements. Frequency tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be provided by treatment groups. All continuous laboratory parameters and vital signs variables at each visit will be summarized by treatment groups. Frequency tables of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values will be provided by treatment groups. Missing safety data will not be imputed.

Long-Term Safety Analysis

Long-term safety analyses that account for protocol-defined treatment switching include reporting of AE rate adjusted by cumulative exposure, descriptive summary in laboratory parameters and vital sign variables by visit, and rate of potentially clinically significant laboratory and vital signs values. The treatment-emergent adverse event (TEAE) rate per 100 patient-years of exposure will be presented by actual treatment received at the time of AE (as described in Section 10.2.2). Listing of subjects with TEAEs by SOC and PT will be provided. Summary statistics for laboratory parameters and vital signs variables at each visit will be presented by "as treated" treatment group sequences defined below. Frequency tables and listings of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values will be provided by actual treatment received at the time of event. Missing safety data will not be imputed.

"As treated" treatment group sequences are defined as follows:

1. Placebo → Upadacitinib 15 mg QD
2. Placebo → Upadacitinib 30 mg QD
3. Upadacitinib 15 mg QD
4. Upadacitinib 30 mg QD

10.2 Analysis of Adverse Events

A treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is after the first dose of study drug, and no more than 30 days after the last dose of study drug.

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an

incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

Adverse event data will be presented by SOCs and PTs using MedDRA Version 19.1 or most up to date version. Adverse event tables will be sorted in alphabetical order by SOC and PT and descending percentages for each treatment group.

10.2.1 Analysis of Adverse Events Prior to Protocol-Defined Treatment Switching

10.2.1.1 Adverse Events Overview

The number and percentage of subjects experiencing TEAEs will be summarized by treatment groups for the following AE categories.

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs of special interest
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

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

For TEAEs of special interest, the point estimate and 95% CI (using normal approximation) will be provided for the treatment difference in AE percentage between each upadacitinib dose group and the combined placebo group.

10.2.1.2 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing adverse events will be tabulated by SOC and PT by treatment groups. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The following summaries of adverse events will be generated:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death
- Frequent AEs (reported in 2% of subjects or more in any treatment group)
- Frequent reasonably possibly related AEs (reported in 2% of subjects or more in any treatment group)

Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

10.2.1.3 TEAEs by Maximum Severity

TEAEs will also be summarized by maximum severity by treatment groups. If a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject has another occurrence of the same event with a severity present. The only exception is that if the subject has another occurrence of the same AE with the most extreme severity – severe. In this case, the subject will be counted under the severe category.

10.2.1.4 TEAEs by Relationship

TEAEs will also be summarized by relationship to upadacitinib and placebo, as assessed by the investigator, by treatment groups. If a subject has a TEAE with an unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same TEAE with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

10.2.1.5 Frequent (≥ 2%) Adverse Events and Reasonably Possibly Related Adverse Events by System Organ Class and Preferred Term

TEAEs and reasonably possibly related AEs occurring for more than 2% of the subjects in any of the treatment groups will be summarized by PT in decreasing frequency separately.

10.2.1.6 Adverse Events of Special Interest

The Adverse Events of Special Interest (AESI) categories will be summarized and presented by treatment groups using SOC and PT. The AESI categories will be identified by the following search criteria per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs) in Table 9 below. Adjudicated cardiovascular events will be summarized and presented by treatment group using the CAC adjudicated categories.

Table 9. AESI for Upadacitinib with SMQs/CMQs/PTs Searches

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Serious Infections	CMQ		"Infections" – Subset for SAEs
Opportunistic Infection	CMQ		"Opportunistic Infection"
Malignancy	SMQ	Narrow	"Malignancies"
Possible Malignancy	SMQ		"Malignant tumours"
Non-Melanoma Skin Cancer (NMSC)	SMQ	Broad	Skin Malignant tumours (Broad SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			"Malignant tumours" SMQ removing NMSC output
Lymphoma	SMQ		"Malignant Lymphomas"
Hepatic Disorder	SMQ	Narrow	"Drug Related Hepatic Disorders"
Gastrointestinal Perforations	SMQ	Narrow	"Gastrointestinal Perforation"
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity – Lymphopenia (Veliparib Product Specific)"
Herpes Zoster	CMQ		"Herpes Zoster"
Creatine Phosphokinase (CPK) Elevation	PT		Search only for the PT of "Blood creatine phosphokinase increased"
Renal Dysfunction	SMQ	Narrow	"Acute Renal, Failure"
Tuberculosis	CMQ		"Tuberculosis"
Adjudicated Cardiovascular Events	Output from CAC		
MACE*			

Table 9. AESI for Upadacitinib with SMQs/CMQs/PTs Searches (Continued)

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Undetermined/Unknown Cause of Deaths			
Other Cardiovascular events			
Venous Thromboembolic Events**			
Other Venous Thrombosis			
Arterial Thromboembolic Events (non-cardiac, non-neurologic)			

* MACE; Major Adverse Cardiovascular Events, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

** Venous thromboembolic events (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE).

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

10.2.2 Analysis of Long-Term Adverse Event Rates

Long-term adverse event rates will be analyzed using event rates adjusted by cumulative exposure and will be based on the actual treatment received at the time of AE occurrence. The detailed treatment groups are defined as follows.

1. Placebo
2. Any upadacitinib 15 mg QD

   This includes AEs which occurred under upadacitinib 15 mg QD exposure from subjects starting on upadacitinib 15 mg QD and subjects switching from placebo to upadacitinib 15 mg QD.
3. Any upadacitinib 30 mg QD

This includes AEs which occurred under upadacitinib 30 mg QD exposure from subjects starting on upadacitinib 30 mg QD and subjects switching form placebo to upadacitinib 30 mg QD.

For event rate calculation, 1 year will be considered to be 365.25 days. For each treatment group, the numerator of the event rate will be the total number of TEAEs reported for the event; that is, a subject can contribute more than one event to the numerator. For each treatment group, the denominator of the event rate will be the total number of days exposed to study drug summed across all treated subjects divided by 365.25. Please refer to Section 8.1 for the calculation of study drug exposure. The TEAE rate per 100 patient-years of exposure will be calculated as ([numerator/denominator])*100. The number of TEAEs reported (numerator), the total number of years of study drug exposure (denominator), and the AE rate per 100 patient-years will be presented for each treatment group.

10.2.2.1 Overview of Adverse Events Rates per 100 Patient-Years of Study Drug Exposure

An overview of AEs per 100 patient-years of study exposure will be presented by treatment group for the following AE categories.

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs of special interest
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

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

For TEAEs of special interest, the point estimate and 95% CI (using normal approximation, refer to Appendix B) will be provided for the treatment difference in AE rate per 100 patient-years between each upadacitinib dose group and the combined placebo group.

10.2.2.2 Adverse Events Rates per 100 Patient-Years of Study Drug Exposure by SOC and PT

For each treatment group, the TEAE rate per 100 patient-years of exposure will be calculated overall, for each SOC and each PT, for each of the following AE categories:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

10.2.2.3 Adverse Events of Special Interest Rates per 100 Patient-Years of Study Drug Exposure by SOC and PT

The Adverse Events of Special Interest (AESI) categories will be summarized and presented for each treatment group using SOC and MedDRA PT, for each of the AESI listed in Section 10.2.1.6. The AESI categories will be identified per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs). Adjudicated cardiovascular events will be summarized and presented by treatment group using the CAC adjudicated categories.

10.2.2.4 Listing of Serious Adverse Events (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All serious adverse events (SAEs), deaths, and adverse events leading to discontinuation of study drug will be listed.

10.3 Analysis of Laboratory Data

10.3.1 Variables and Units

All laboratory parameters to be collected in this study are listed below. Laboratory parameters will be reported using the standard international (SI) units.

Table 10. List of Laboratory Variables

Laboratory Variables
Hematology
White Blood Cell (WBC) Count
Red Blood Cell (RBC) Count
Hemoglobin
Hematocrit
Platelet count
Neutrophils
Basophils
Eosinophils
Lymphocytes
Monocytes
Bands
Chemistry
Total Bilirubin
Alkaline Phosphatase (ALP)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total Protein
Albumin
Glucose
Triglycerides
Blood Urea Nitrogen (BUN)
Creatinine
Uric acid
Sodium
Potassium
Calcium
Inorganic Phosphorus
Creatine Phosphokinase (CPK)
Chloride
Bicarbonate

Table 10. List of Laboratory Variables (Continued)

Laboratory Variables
Chemistry (Continued)
Cholesterol
LDL cholesterol
HDL cholesterol
LDL/HDL ratio
Cholesterol/HDL ratio
Urinalysis
Specific Gravity
pH
Protein
Glucose
Ketones
Blood
Microscopic Examination (if needed)
Urobilinogen
Bilirubin
Leukocytes
Nitrites
Other
hs-CRP
ESR

10.3.2 Analysis of Laboratory Data Through Week 24

The laboratory data will be summarized by the treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD, and the combined placebo group).

10.3.2.1 Assessment of Clinical Laboratory Variables

Analyses of hematology, chemistry, and urinalysis variables which are measured longitudinally will be performed by visits and by treatment groups. For analysis at each

visit, the following summary statistics of visit values will be presented for each treatment group: sample size, mean, standard deviation, minimum, median, and maximum.

An ANOVA model with treatment as a factor will be used to compare change and percentage change from baseline between different treatment groups for selected laboratory parameters. Mean difference from placebo and associated 95% CIs will be presented. The analysis applies to the following laboratory parameters of clinical interest: hemoglobin, platelets, lymphocytes, neutrophils, creatinine, creatine phosphokinase (CPK), LDL, HDL, the ratio of LDL to HDL, and total cholesterol.

10.3.2.2 Assessment of Shift from Baseline in Clinical Laboratory Variables

The baseline and post-baseline laboratory observations will be categorized as Low, Normal, and High according to normal ranges. The shift tables will tabulate the number and percentage of subjects with baseline and post-baseline values by these categories.

For each laboratory variable, shift tables will be generated that cross tabulate the subjects' as deemed appropriate by treatment groups:

- Shift from baseline high or normal to minimum post-baseline low; shift from baseline low or normal to maximum post-baseline high.
- Shift from baseline high or normal to final post-baseline low; shift from baseline low or normal to final post-baseline high.

Note that the minimum/maximum category is used, rather than the category of the minimum/maximum value. The two may be different due to variation in the reference range.

No statistical tests will be performed for this analysis.

10.3.2.3 Assessment of Potentially Clinical Significant Laboratory Values

The criteria for potentially clinically significant laboratory values will be determined by CTCAE criteria of Grade 3 or above. The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory values will be summarized by treatment groups.

10.3.2.4 Assessment of Liver Elevations

According to FDA's Guidance for Industry "Drug-Induced Liver Injury: Premarketing clinical evaluation" (July 2009), when aminotransferase abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation > 2 × ULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI.

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest will be summarized by treatment groups:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- TBL ≥ 2 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN

- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN

10.3.3 Analysis of Long-Term Laboratory Data

10.3.3.1 Assessment Clinical Laboratory Variables

Analyses of hematology, chemistry, and urinalysis variables which are measured longitudinally will be performed by visits and by treatment group sequences as described in Section 10.1. For each analysis, the following summary statistics of visit values will be presented for each treatment group sequence: sample size, mean, standard deviation, minimum, median and maximum.

Analyses will be performed for change and percentage change from baseline in hemoglobin, lymphocytes, neutrophils, creatinine, and creatine phosphokinase (CPK).

10.3.3.2 Assessment of Potentially Clinical Significant Laboratory Values

Long-term laboratory data will be summarized based on the number and percentage of subjects meeting the criteria for potentially clinical significant laboratory values and by the actual treatment received at the time of the event occurrence. The treatment groups are the same as the ones for long-term AE analysis as described in Section 10.2.2. A subject can be counted under different treatment groups if he/she was on placebo from baseline to Week 24 and then started upadacitinib 15 or 30 mg at Week 24 and experienced potentially clinical significant laboratory values under different treatment groups.

In the evaluation of potentially clinically significant laboratory values, the baseline value will be determined by the last non-missing measurement recorded on or before the date of the first dose of study drug in the corresponding treatment group (which may be different than the first dose of study drug received in the study). For example, for a subject who started on placebo and switched to upadacitinib 15 mg QD at Week 24, lab values under

upadacitinib 15 mg QD exposure would be evaluated against the baseline value defined as the last non-missing measurement recorded on or before the date of the first dose of upadacitinib 15 mg QD.

A listing of all subjects with any laboratory determination meeting CTCAE criteria of Grade 3 or above will be provided by Grade. For each of these subjects, the whole course of the respective parameter will be listed.

10.3.3.3 Assessment of Liver Elevations

The frequencies and percentages of subjects with post-baseline liver-specific function test values that meet the following criteria of potential clinical interest will be summarized by the actual treatment received at the time of the event occurrence, as described in Section 10.2.2.

A subject can be counted under different treatment groups if he/she was on placebo from baseline to Week 24 and then started upadacitinib 15 or 30 mg at Week 24 and experienced potentially clinical significant laboratory values under different treatment groups.

A listing of potentially clinically significant liver elevations based on criteria specified above will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

10.4 Analysis of Vital Signs

10.4.1 Variables and Criteria Defining Abnormality

Vital sign variables include sitting systolic blood pressure, sitting diastolic blood pressure, pulse rate, and weight. The criteria for potentially clinically significant vital sign findings are presented in Table 11.

Table 11. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 15 mmHg from Baseline
	High	Value ≥ 105 mmHg and increase ≥ 15 mmHg from Baseline
Pulse	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Weight	High	> 7% increase from baseline
	Low	> 7% decrease from baseline

10.4.2 Analysis of Vital Signs Through Week 24

Analyses of vital sign variables which are measured longitudinally will be performed by visits and by the treatment groups of upadacitinib 15 mg QD, upadacitinib 30 mg QD, and the combined placebo group. For each analysis, the following summary statistics will be presented for each treatment group: sample size, mean, standard deviation, minimum, median, and maximum.

The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized by treatment groups.

10.4.3 Analysis of Long-Term Vital Signs

Analyses of vital signs variables which are measured longitudinally will be performed by visits and by treatment group sequences as described in Section 10.1. For each analysis, the following summary statistics will be presented for each treatment group: sample size, mean, standard deviation, minimum, median, and maximum.

Long-Term vital signs will also be summarized based on the number and percentage of subjects meeting the criteria for potentially clinical significant vital sign values and by the actual treatment received at the time of the event occurrence. The treatment groups are the same as the ones for long-term AE analysis as described in Section 10.2.2. A subject

can be counted under different treatment groups if he/she was on placebo from baseline to Week 24 and then started upadacitinib 15 or 30 mg at Week 24 and experienced potentially clinical significant laboratory values under different treatment groups. In the evaluation of potentially clinically significant vital sign values, the baseline value will be determined by the last non-missing measurement recorded on or before the date of the first dose of study drug in the corresponding treatment group, similarly as described in Section 10.3.3.2.

A listing of all subjects with any vital sign values meeting the criteria for potentially clinically significant vital signs will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

11.0 References

1. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.
2. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.
3. Greenland S, Rothman KJ. Introduction to stratified analysis. In: Rothman KJ, Greeland S, Lash TL, editors. Modern Epidemiology, 3rd Edition. Philaphdelphia: Lippincott Williams & Wilkins; 2008.
4. Liu GF, Wang J, Liu K, et al. Confidence intervals for an exposure adjusted incidence rate difference with application to clinical trials. Stat Med. 2006;25(8):1275-86.

Appendix A. SAS Procedure for Mantel-Haenszel Test

A SAS procedure, the STDRATE, will be used to compute the statistics using the Mantel-Haenszel method (Greenland and Rothman 2008, p. 271). Risk difference, 95% CI and p value will be provided through the program.

SAS code example:

```
ods graphics on;
proc stdrate data=ACR20_Week12
             method=mh
             stat=risk
             effect=diff
             plots=all
                  alpha=0.05
             ;
                  where TRTP='PLACEBO' | TRTP='UPA 30MG";
   population group=TRTP event=RESPONDERS total=COUNT;
   strata DMARDUSE / order=data stats effect;
run;
```

Note: input data set is a summary level of data at Week 12 including treatment, stratum, ACR20 responders and total number of subjects per stratum and treatment. "RESPONDERS" is the total number of ACR20 responders and the "COUNT" is the total number of subjects per stratum and treatment.

Appendix B. Exposure Adjusted AE Rate Difference and Normal Approximation Based 95% Confidence Interval (Liu, F et al. 2006)

Assume the occurrence of TEAE of special interest follows a Poisson distribution and let λ denote the rate of occurrence of TEAE under the total exposure time for a treatment group. Let n_1 and n_2 be the number of AEs reported in an upadacitinib dose group and the combined placebo group, respectively. Let T_1 and T_2 be the total number of days exposed to study drug summed across all treated subjects in an upadacitinib dose group and the combined placebo group. Under the assumption that n1 and n2 follow independent Poisson distribution with parameters $\lambda_1 T_1$ and $\lambda_2 T_2$, the $\hat{\lambda}_1 = n_1/T_1$ and $\hat{\lambda}_2 = n_2/T_2$. So the exposure adjusted TEAE rate difference can be estimated by

$$\theta = \hat{\lambda}_1 - \hat{\lambda}_2$$

Using normal approximation, the 95% confidence interval can be calculated by

$$\hat{\lambda}_1 - \hat{\lambda}_2 \pm Z_{\alpha/2}\hat{\sigma}$$

where $\hat{\sigma} = \sqrt{n_1/T_1^2 + n_2/T_2^2}$

Document Approval

Study M15554 - Statistical Analysis Plan Version 1 - 12Apr2018 (E3 16.1.9)

Version: 1.0 **Date:** 13-Apr-2018 03:27:10 PM **Company ID:** 04132018-00F9F683CEE7AB-00001-en

Signed by:	Date:	Meaning Of Signature:
PPD	12-Apr-2018 05:26:42 PM	Approver
	12-Apr-2018 05:42:26 PM	Author
	13-Apr-2018 02:19:08 AM	Approver
	13-Apr-2018 03:27:10 P	Approver

1.0 Title Page

Statistical Analysis Plan

Study 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***

Date: 02 Oct 2019

Version 2.0

2.0 Table of Contents

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the Data and Statistical Science Department for upadacitinib Study M15-554. It provides details to further elaborate statistical methods as outlined in the protocol. Pharmacokinetic and biomarker analyses will be performed separately and are not in the scope of this SAP.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Study 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 biologic DMARDs (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 biologic DMARDs.

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.

4.2 Overall Study Design and Plan

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 active 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.

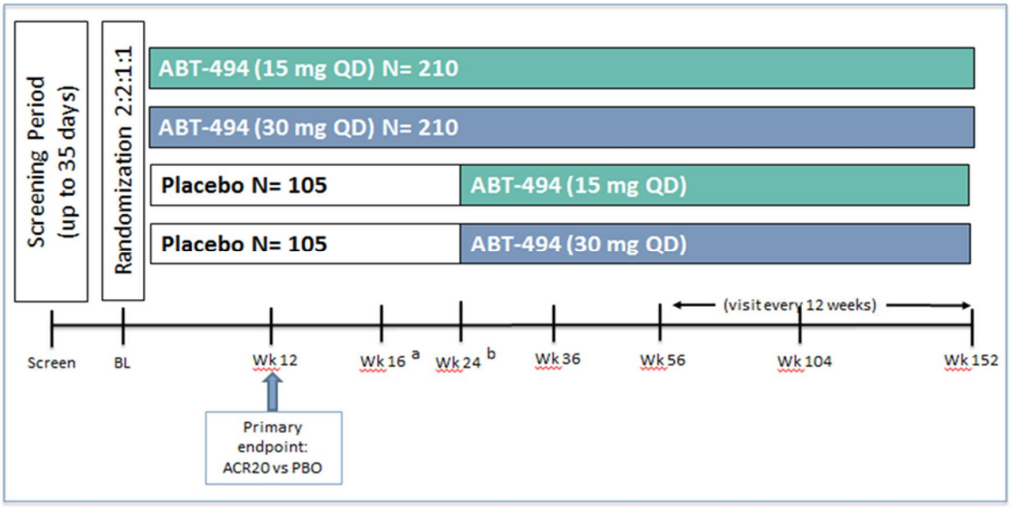
Subjects who meet eligibility criteria will be randomized in a 2:2:1:1 ratio using an Interactive Response Technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: Upadacitinib 15 mg QD, N = 210)
- Group 2: Upadacitinib 30 mg QD, N = 210)
- Group 3: Placebo, N = 105 (Day 1 to Week 24) → Upadacitinib 15 mg QD (Week 24 and thereafter)
- Group 4: Placebo, N = 105 (Day 1 to Week 24) → Upadacitinib 30 mg QD (Week 24 and thereafter)

Randomization will be stratified by extent of psoriasis (≥ 3% body surface area [BSA] or < 3% BSA), current use of at least 1 DMARD (Yes or No), and number of prior failed 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.

A schematic of the overall study design is shown in Figure 1 below. For a more detailed description of the study design, refer to Section 5.0 of the most up-to-date version of the study protocol.

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 of the most up-to-date version of the study protocol.

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

4.3 Sample Size

The planned total 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 a two-sided significance level of 0.025 and accounting for a 10% dropout rate.

4.4 Week 24 Analysis and Data Base Lock

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 (Period 1), study sites and subjects will remain blinded until all subjects have reached Week 56.

4.5 Data Monitoring Committee (DMC) Activities

An independent external Data Monitoring Committee (DMC) is used to review unblinded safety data at regular intervals during the conduct of the study. The DMC will provide recommendation to an AbbVie Point of Contact on whether to continue, modify, or terminate studies after each review. When needed, high-level unblinded efficacy data may also be requested by the DMC and be reviewed so that the DMC can assess benefit:risk of any emerging safety differences.

5.0 Analysis Populations and Analysis Windows

5.1 Analysis Populations

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.

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 any major protocol deviations that are determined to have a potential impact on the primary efficacy endpoint up to Week 12 in Period 1 of the study. Additional analysis of the primary efficacy endpoint will be conducted on the Per Protocol analysis set, in order to evaluate the impact of protocol deviations.

Protocol deviations with potential to affect the primary efficacy endpoint (key ICH deviations and other clinically significant non-ICH deviations) will be identified prior to the Week 24 database lock.

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 will be analyzed "as treated," regardless of the treatment randomized. "As treated" is determined by the treatment the subject received during the majority of the subject's drug exposure time in the analysis period.

5.2 Analysis Windows

Definition of Study Days (Days Relative to the First Dose of Study Drug)

Study Days are calculated for each collection date relative to the date of the first dose of study drug. It is defined as the number of days between the date of the first dose of study drug and the collection date. Study days are negative values when the collection date of interest is prior to the first study drug dose date. Study days are positive values when the collection date of interest is on or after the first study drug dose date. The day of the first dose of study drug is defined as Study Day 1, while the day prior to the first study drug dose is defined as Study Day –1 (there is no Study Day 0). Study days are used to map actual study visits to the protocol-specified study visits.

Definition of Analysis Windows

The following rules will be applied to assign actual subject visits to protocol-specified visits. For each protocol-specified study visit, a target study day will be identified to represent the corresponding visit along with a window around the target day. Windows will be selected in a non-overlapping fashion so that a collection date does not fall into multiple visit windows. If a subject has two or more actual visits in one visit window, the visit closest to the target day will be used for analysis. If two visits are equidistant from the target day, then the later visit will be used for analysis.

The visit window and the target study day for each protocol-specified visit in Period 1 are displayed in Table 1 to Table 5 (depending on the different visit schedules of different endpoints). Visit windows for protocol-specified visits in Period 2 are defined similarly.

Table 1. Analysis Windows for Efficacy Analysis for Period 1 (for ACR Components, TJC28, SJC28, ESR and Derived Endpoints[a]) and Safety Analysis for Period 1 (for Lab Values [Clinical Chemistry, Hematology, Urinalysis] and Vital Signs/Weight)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
2	2	15	22
4	23	29	43
8	44	57	71
12	72	85	99
16	100	113	127
20	128	141	155
24	156	169	Min (183, first dose date from Week 24 dispensed kit)
28	Min (183, first dose date from Week 24 dispensed kit) + 1	197	211
32	212	225	239
36	240	253	281
44	282	309	351
56	352	393	435

a. ACR20/50/70 response rates, DAS28 (CRP), DAS28 (ESR), PsARC, DAPSA, proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35).

b. Day of first dose of study drug.

Table 2. Analysis Windows for Efficacy Analysis for Period 1 (for SF-36, EQ-5D-5L, FACIT-F, WPAI, BASDAI, HRU and Derived Endpoints[a])

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
12	2	85	127
24	128	169	Min (211, first dose date from Week 24 dispensed kit)
36	Min (211, first dose date from Week 24 dispensed kit) + 1	253	323
56	324	393	435

a. PASDAS, BASDAI 50 response rates, Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6), ASDAS, proportion of subjects with ASDAS Inactive Disease, proportion of subjects with ASDAS Major Improvement, proportion of subjects with ASDAS Clinically Important Improvement.

b. Day of first dose of study drug.

Table 3. Analysis Windows for Safety Analysis for Period 1 (for Total Cholesterol, HDL-C, LDL-C, Triglycerides, Advanced Lipid Testing[a])

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
4	2	29	57
12	58	85	127
24	128	169	Min (211, first dose date from Week 24 dispensed kit)

a. Advanced lipid testing is exploratory and may not be performed and/or be reported in the CSR.

b. Day of first dose of study drug.

Table 4. Analysis Windows for Efficacy Analysis for Period 1 (for BSA-Psoriasis, PASI, sIGA, LDI, LEI, SPARCC Enthesitis Index and Derived Endpoints[a])

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[b]	1
12	2	85	99
16	100	113	141
24	142	169	Min (211, first dose date from Week 24 dispensed kit)
36	Min (211, first dose date from Week 24 dispensed kit) + 1	253	323
56	324	393	435

a. MDA, dactylitis count/total enthesitis count, proportion of subjects with resolution of dactylitis/enthesitis (out of all sites, or the sites included in SPARCC or LEI), PAISI75/90/100, 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.

b. Day of first dose of study drug.

Table 5. Analysis Windows for Efficacy Analysis for Period 1 (for SAPS)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
16	2	113	141
24	142	169	Min (211, first dose date from Week 24 dispensed kit)
36	Min (211, first dose date from Week 24 dispensed kit) + 1	253	323
56	324	393	435

a. Day of first dose of study drug.

6.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

6.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics information will be collected at the Baseline visit of the study and will be summarized for the FAS. The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables. Categorical or discrete variables will be summarized via frequencies and percentages. Summary statistics will be computed for each treatment group and overall.

Main Demographic and Baseline Characteristics

- Sex (male, female)
- Age (years)
- Age Categories (< 65, 65 - < 75, ≥ 75 years)
- Race (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Geographic Region (North America, Western Europe and Oceania, Eastern Europe, Latin-America, Asia, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Body Mass Index (BMI) Category (kg/m^2) (BMI < 25, BMI ≥ 25)

PsA Medical History, Prior and Baseline Treatments

- Duration of PsA symptoms in years
- Duration of PsA diagnosis in years
- Rheumatoid Factor (RF) status: Positive or Negative
- Anti-CCP status: Positive or Negative

- Number of prior non-biologic DMARDs (0, 1, 2, ≥ 3)
- Number of prior biologic DMARDs (0, 1, 2, ≥ 3)
- Number of prior biologic DMARDs other than anti-TNF (0, 1, 2, ≥ 3)
- Number of prior anti-TNFs (0, 1, 2, ≥ 3)
- Number of prior failed biologic DMARDs (0, 1, 2, ≥ 3)
- Current use of at least 1 non-biologic DMARD at baseline (Yes or No)
- Current NSAID use at baseline (Yes or No)
- Current Corticosteroid use at baseline (Yes or No)
- Concomitant non-biologic DMARD at baseline (MTX alone, MTX and other non-biologic DMARD, non-biologic DMARD other than MTX)

Baseline Disease Characteristics

- Tender joint count (TJC68) defined as the number of tender joints out of 68 assessed joints
- Swollen joint count (SJC66) defined as the number of swollen joints out of 66 assessed joints
- Physician's global assessment of Disease Activity Numeric Rating Scale (0 - 10 NRS)
- Patient's assessment of pain (0 - 10 NRS)
- Patient's assessment of disease activity (0 - 10 NRS)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- High sensitivity C-reactive protein (hsCRP)
- Categories for hsCRP: equal or below vs. above ULN (2.87 mg/L)
- Body Surface Area (BSA) with Psoriasis (as categorical with < 3%, ≥ 3%)
- Body Surface Area (BSA) with Psoriasis (as continuous for subjects with BSA-Ps > 0%)
- Static Investigator Global Assessment of Psoriasis (sIGA) (as a categorical variable)
- Psoriasis Area and Severity Index (PASI) score (for subjects with ≥ 3% Body Surface Area (BSA) psoriasis)

- Erythrocyte sedimentation rate (ESR)
- Psoriatic arthritis disease activity score (PASDAS)
- Disease Activity In Psoriatic Arthritis (DAPSA) score
- Presence of Dactylitis (defined as LDI > 0)
- Leeds Dactylitis Index (LDI) (out of subjects with presence of dactylitis (LDI > 0))
- Total dactylitis count (out of subjects with presence of dactylitis (LDI > 0))
- Presence of Enthesitis (defined as total enthesitis count > 0)
- Total enthesitis count (out of subjects with presence of enthesitis (total enthesitis count > 0))
- Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (out of subjects with SPARCC Enthesitis Index > 0)
- Leeds Enthesitis Index (LEI) (out of subjects with LEI > 0)
- DAS28 [CRP]
- DAS28 [ESR]
- Presence of Psoriatic Spondylitis
- Ankylosing Spondylitis Disease Activity Score (ASDAS) (out of subjects with presence of psoriatic spondylitis)
- Bath AS Disease Activity Index (BASDAI) (out of subjects with presence of psoriatic spondylitis)
- Morning stiffness (mean of BASDAI Questions 5 and 6)
- Morning stiffness severity 0-10 (BASDAI Question 5)
- Morning stiffness duration 0-10 (BASDAI Question 6)

Patient Report Outcomes at Baseline

- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
- 36-Item Short Form Health Survey (SF-36) Version 2: physical component summary, mental component summary, and the 8 sub-domain scores
- EuroQol-5D-5L (EQ-5D-5L) index and VAS score
- Work Productivity and Activity Impairment (WPAI)

- Self-Assessment of Psoriasis Symptoms (SAPS)

Tobacco/Nicotine and Alcohol Use

- Tobacco/Nicotine Use [user, ex-user, non-user, unknown]
- Alcohol Use [drinker, ex-drinker, non-drinker, unknown]

6.2 Medical History

Medical history data will be summarized and presented for FAS population using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each randomized treatment group as well as overall. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system. No statistical comparison will be performed for medical history reporting.

6.3 Prior Treatment and Concomitant Medications

Prior and concomitant medications will be summarized by each randomized treatment group as well as overall for FAS. Prior medications are those medications taken prior to the first dose of study drug. This includes medications with a start date before the first study drug administration date, regardless of the end date of these medications. Medications taken on the day of the first dose of study drug are not counted as prior medications. Concomitant medications are those medications, other than study drug, taken after the first dose of study drug and within 1 day of the last dose of study drug. This includes medications with a start date between first study drug administration and last study drug administration + 1 day, as well as, medications with a start date prior to first dose of study drug and which are ongoing after first dose of study drug. Medications taken on the day of the first dose of study drug are counted as concomitant medications.

The number and percentage of subjects who received a prior medication and the number and percentage of subjects who received a concomitant medication will be tabulated separately by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary.

6.4 Protocol Deviations

Protocol deviations based on ICH deviation criteria are categorized as follows:

1. Those who entered the study even though they did not satisfy the entry criteria
2. Those who developed withdrawal criteria during the study and were not withdrawn
3. Those who received the wrong treatment or incorrect dose, and
4. Those who received an excluded or prohibited concomitant medication.

The protocol deviations listed above will be summarized and listed by treatment group.

7.0 Patient Disposition

The following will be summarized by randomized treatment group as well as overall:

- number of subjects randomized,
- number of subjects included in key analysis populations (Full Analysis Set and Per Protocol Analysis Set for efficacy analysis, Safety Analysis Set for safety analysis),
- number of subjects who completed Period 1 study participation,
- number of subjects who entered Period 2,
- number of subjects who completed overall study (Period 1 and Period 2) participation (if applicable).

Premature discontinuation details will be further summarized separately for Period 1 and Period 2 as follows.

Period 1

The number and percentage of subjects who completed Period 1 and prematurely discontinued in Period 1 will be summarized by randomized treatment group, separately by study drug completion/discontinuation and by study participation completion/discontinuation, with the reason for discontinuation collected from the CRF by the following categories:

- Adverse event (AE)
- Withdrew consent
- Lost to follow-up
- Lack of efficacy
- Other.

In addition, the number and percentage of subjects entered Period 2 will be summarized by randomized treatment group.

For Week 24 reporting, this summary will also be presented for study drug completion/discontinuation by Week 24.

Period 2

Period 2 patient dispositions and reason for discontinuation will be summarized with the same categories as given above for Period 1 for overall total and by treatment in Period 2, defined as follows:

1. Upadacitinib 15 mg QD
2. Upadacitinib 30 mg QD

Among the subjects who entered Period 2 participation (regardless of whether subject entered Period 2 on study drug), the number and percentage of subjects who completed and prematurely discontinued study participation in Period 2 will be summarized.

Among the subjects who entered Period 2 on study drug, the number and percentage of subjects who completed and prematurely discontinued study drug in Period 2 will be summarized.

8.0 Study Drug Exposure and Compliance

8.1 Study Drug Exposure

For short term up to Week 24, the duration of exposure to study drug will be summarized for the safety analysis set by the randomized treatment groups.

For long term, the duration of exposure to study drug will be summarized for the safety analysis set by the following groups.

1. Upadacitinib 15 mg QD

   This includes upadacitinib 15 mg QD exposure from subjects starting on upadacitinib 15 mg QD and subjects switching from placebo to upadacitinib 15 mg QD.

2. Upadacitinib 30 mg QD

   This includes upadacitinib 30 mg QD exposure from subjects starting on upadacitinib 30 mg QD and subjects switching from placebo to upadacitinib 30 mg QD.

Exposure to upadacitinib and placebo is defined as last dose date minus first dose date plus 1 day.

The duration of exposure to study drug will be summarized for each group as specified above, with the number of subjects, mean, standard deviation, median, minimum and maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following cumulative duration intervals.

- $\geq$ 2 weeks

- ≥ 1 month
- ≥ 3 months
- ≥ 6 months
- ≥ 9 months
- ≥ 12 months
- ≥ 18 months
- ≥ 2 years
- ≥ 2.5 years

8.2 Compliance

Study drug compliance will be summarized for each treatment group at Week 24. The compliance is defined as the number of tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) during the subject's participation up to Week 24 divided by the number of days that the subject was in the Treatment Phase up to Week 24.

9.0 Efficacy Analysis

9.1 General Considerations

There are two sets of planned efficacy analysis: efficacy analysis through Week 24 and long-term efficacy analysis. Unless otherwise noted, all efficacy analyses will be carried out using the FAS population.

9.1.1 Efficacy Analysis at Different Phases of the Study

Efficacy Analysis Through Week 24

Efficacy analysis by randomized treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD and the combined placebo group) will be performed on efficacy data up to Week 24. No protocol-defined treatment switching will occur prior to the time point.

Formal statistical inference will be generated, and results from this set of analysis will be used as the key efficacy findings of this study.

Long-Term Efficacy Analysis

Long-term efficacy analysis will be performed on As Observed data (defined in Section 9.1.2) by randomized treatment group sequence as described below:

1. Placebo → Upadacitinib 15 mg QD
2. Placebo → Upadacitinib 30 mg QD
3. Upadacitinib 15 mg QD
4. Upadacitinib 30 mg QD

Descriptive statistics and 95% confidence intervals will be provided for all treatment sequences.

9.1.2 Handling of Missing Data and Intercurrent Events

Non-Responder Imputation (NRI) Approach

The NRI approach will handle data for binary endpoints as follows.

- Subjects who prematurely discontinue from study drug will be considered as non-responders for all subsequent visits after discontinuation.
- In addition, any subject with any missing value for the binary endpoints at a specific visit will be treated as non-responder for that visit.

NRI data handling will be used for the primary estimand (refer to Section 9.2.1) for the binary endpoints.

Mixed-Effects Model Repeated Measures (MMRM)

The repeated measure analysis will be conducted using mixed models including observed data at all visits. For the MMRM analysis, data collected after premature discontinuation

of study drug will be excluded. The mixed model includes the categorical fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor current DMARD use (yes/no) and the continuous fixed covariates of baseline measurement. An unstructured variance covariance matrix will be used. The parameter estimations are based on the assumption of data being missing at random (MAR) and using the method of restrictive maximum likelihood (REML). MMRM will be used for the primary estimand of key continuous endpoints (refer to Section 9.2.3).

As Observed (AO)

The AO data handling 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 AO analysis for that visit. Regardless of premature discontinuation of study drug or use of rescue medication, all observed data will be used in the analysis. The AO data handling will be used to facilitate the supplementary analysis for both binary and continuous endpoints (refer to Section 9.2.2 and Section 9.2.3 where the corresponding supplementary estimands for the primary and ranked secondary endpoints are described respectively).

The intent-to-treat (ITT) principle for the analysis using AO data, AO (with imputation), where additional missing data will be imputed as non-responders, will be used for the supplementary analysis of the primary and key secondary binary endpoints.

9.2 Efficacy Analysis Through Week 24

9.2.1 Primary Efficacy Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is ACR20 response at Week 12. The primary estimand is the difference in the proportion of PsA patients who achieved ACR20 response at Week 12 and did not discontinue study drug by Week 12, comparing those who are randomized to each upadacitinib dose group and received study drug to those who are randomized to placebo and received study drug.

Analysis of the primary endpoint will be conducted on the FAS based on randomized treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD versus the combined placebo groups). Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Comparisons of the primary endpoint will be made between each upadacitinib dose and the combined placebo group using the Cochran-Mantel-Haenszel test (CMH) (refer to Appendix A) adjusting for the main stratification factor of current DMARD use (yes/no). Point estimate, 95% CI using normal approximation and p-value for the treatment comparison will be presented. Nominal p-values constructed using the CMH test will be provided. The multiplicity adjusted (as described in Section 9.2.5) testing results will also be provided. NRI data handling will be used to facilitate the primary estimand. In addition, the number and percentage of non-responders by the intercurrent events, such as discontinuation of study drug prior to or at Week 12 or missing Week 12 ACR measurement will be summarized.

9.2.2 Supplementary Analysis of the Primary Efficacy Endpoint

For the primary efficacy endpoint, the same CMH analysis as detailed in Section 9.2.1 will be repeated using As Observed (AO) data handling without any imputation as supplementary analysis. This will be conducted on the FAS based on randomized treatment groups. The corresponding estimand for the supplementary analysis is the difference in the proportion of PsA patients who achieved ACR20 response at Week 12, regardless of whether the subject had discontinued study drug by Week 12, comparing each upadacitinib dose group vs placebo. The analysis will be conducted for those who are randomized, received study drug and have the efficacy measurement at Week 12 visit.

In addition to the supplementary analysis based on AO data, to explore various missing data assumptions including missing not at random (MNAR), tipping point analysis will also be performed for the primary endpoint by multiple imputations using logistic regression, allowing the imputed ACR response rate to systematically vary from 0% to 100% in both upadacitinib and placebo, respectively. Details of the tipping point analysis are outlined in Appendix B. Supportive analysis will also be conducted on the Per Protocol Analysis Set using the CMH model and NRI data handling.

9.2.3 Key Secondary Efficacy Analyses

The following is a list of ranked key secondary endpoints:

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 (for subjects with baseline sIGA ≥ 2);
3. Psoriasis Area Severity Index (PASI) 75 response at Week 16 (for subjects with $\geq 3\%$ BSA psoriasis at baseline);
4. Change from baseline in SF-36 PCS at Week 12;
5. Change from baseline in FACIT-Fatigue 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) at Week 16.

Additional key secondary efficacy endpoints are:

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

Binary Endpoints

For binary endpoints, frequencies and percentages will be reported for each treatment group. For the ranked secondary endpoints at the time point of interest, the primary estimand is the same as that for the primary efficacy endpoint as defined in Section 9.2.1, except for the definition of the efficacy measurement.

For secondary endpoints applicable only for sub-populations, the estimands will be constructed similarly but based on the subject sub-population, as defined in the below table.

Endpoint	Sub-population
Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline at Week 16	Subjects with baseline sIGA ≥ 2 are included in the analysis
Psoriasis Area Severity Index (PASI) 75 response at Week 16	Subjects with ≥ 3% BSA psoriasis at baseline are included in the analysis

For MDA at Week 24, in addition to the NRI data handling as defined in Section 9.1.2, subjects who meet the rescue criteria (i.e., 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 also be treated as non-responders. The corresponding primary estimand is the difference in the proportion of patients who achieved MDA at Week 24, and who did not discontinue study drug and did not initiate rescue therapy by Week 24. The comparison is for each upadacitinib dose group vs placebo for patients randomized and treated with at least one dose of study drug. Supplementary analysis using AO data handling will also be conducted for binary endpoints. The corresponding supplementary estimand is the same as defined in Section 9.2.2 except for the definition of the efficacy measurement.

Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Treatment comparisons will be made between each upadacitinib dose and the combined placebo group using the Cochran-Mantel-Haenszel test (refer to Appendix A). The CMH test adjusts for the main stratification factor of current DMARD use (yes/no). Point estimate, 95% CI using normal approximation and the p-value for the treatment difference will be presented.

Continuous Endpoints

For continuous endpoints, the estimand is the difference in mean change from baseline at the protocol defined time point (e.g., HAQ-DI at Week 12) under the assumption that patients with missing data, including those due to premature discontinuation of study drug, can have their measurements at the protocol defined time point predicted by their observed data and the observed data for other patients for their respective assessments during follow-up. The comparison is for each upadacitinib dose group vs placebo for patients randomized and treated with at least one dose of study drug.

To analyze the primary estimand for the continuous ranked secondary efficacy endpoints, statistical inference will be conducted using the MMRM model and the associated data handling as described in Section 9.1.2, with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no) and the continuous fixed covariate of baseline measurement. The LS mean and 95% CI for each randomized treatment group and the LS mean treatment difference, the associated 95% CI and the p-value between each upadacitinib dose group and the combined placebo group will be provided.

The supplementary analysis for ranked secondary continuous endpoints will be conducted using AO data handling and using the analysis of covariance (ANCOVA) model with treatment and the stratification factor of current DMARD use (yes/no) as the fixed factors and the corresponding baseline values as the covariates. The corresponding estimand is the difference in the mean change from baseline in the efficacy endpoints at the protocol defined time point regardless of treatment discontinuation or use of rescue medication, comparing each upadacitinib dose group vs placebo. The analysis will be conducted for those who are randomized, received study drug and have the efficacy measurement at the protocol defined time point.

For the key continuous endpoint change from baseline in HAQ-DI at Week 12, tipping point analysis will also be conducted using multiple imputation (MI) as additional supplementary analysis to explore various missing data assumptions including missing not

at random (MNAR). Details of the tipping point analysis for continuous endpoints are outlined in Appendix C.

9.2.4 Efficacy Analyses for Additional Endpoints

Additional efficacy analysis includes the following endpoints at the 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 (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;
- Proportion of subjects achieving MDA;
- Change from baseline in Leeds Dactylitis Index (LDI) (for subjects with baseline LDI > 0);
- Change from baseline in dactylitis count (for subjects with baseline LDI > 0);
- Proportion of subjects with resolution of dactylitis (defined as LDI = 0) (for subjects with baseline LDI > 0);
- Change from baseline in LEI (for subjects with baseline LEI > 0);
- Proportion of subjects with resolution of enthesitis defined as LEI = 0 (for subjects with baseline LEI > 0);
- Change from baseline in SPARCC Enthesitis Index (for subjects with baseline SPARCC Enthesitis Index > 0);

- Proportion of subjects with resolution of enthesitis defined as SPARCC Enthesitis Index = 0 (for subjects with baseline SPARCC Enthesitis Index > 0);
- Change from baseline in total enthesitis count (for subjects with baseline total enthesitis count > 0);
- Proportion of subjects with resolution of enthesitis defined as total enthesitis count = 0 (for subjects with baseline total enthesitis count > 0);
- 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 (for subjects with baseline sIGA ≥ 2);
- Change from baseline in BSA-Ps (for subjects with baseline BSA > 0%);
- 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;
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue;
- Change from baseline in EuroQol-5D-5L (EQ-5D-5L) index and VAS score;
- Change from baseline in Work Productivity and Activity Impairment (WPAI);
- Cumulative Health Resource Utilization (HRU);
- Change from baseline in Self-Assessment of Psoriasis Symptoms (SAPS);
- Change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (out of subjects with presence of psoriatic spondylitis at baseline);
- BASDAI 50 response rates (out of subjects with presence of psoriatic spondylitis at baseline);

- Change from baseline in Morning stiffness (mean of BASDAI Questions 5 and 6)
- Change from baseline in Morning stiffness severity 0 - 10 (BASDAI Question 5)
- Change from baseline in Morning stiffness duration 0 - 10 (BASDAI Question 6)
- Change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects with ASDAS Inactive Disease (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects with ASDAS Major Improvement (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects with ASDAS Clinically Important Improvement (out of subjects with presence of psoriatic spondylitis at baseline);
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI ($\geq$ 0.35).

For binary endpoints, frequencies and percentages will be reported for each treatment group. NRI will be used for primary analysis. AO will be used as supplementary analysis. Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Treatment comparisons will be made between each upadacitinib dose to the combined placebo group using the CMH (refer to Appendix A) test adjusting for the main stratification factor of current DMARD use (yes/no). Point estimate, 95% CI using normal approximation and the nominal p-value for the treatment difference will be presented.

For continuous endpoints, the LS mean and 95% CI for each randomized treatment group and the LS mean treatment difference, the associated 95% CI and the p-value between each upadacitinib dose group and the combined placebo group will be provided using MMRM model as described in Section 9.2.3, with fixed effects of treatment, visit, treatment-by-visit interaction, the stratification factor of current DMARD use (yes/no) and

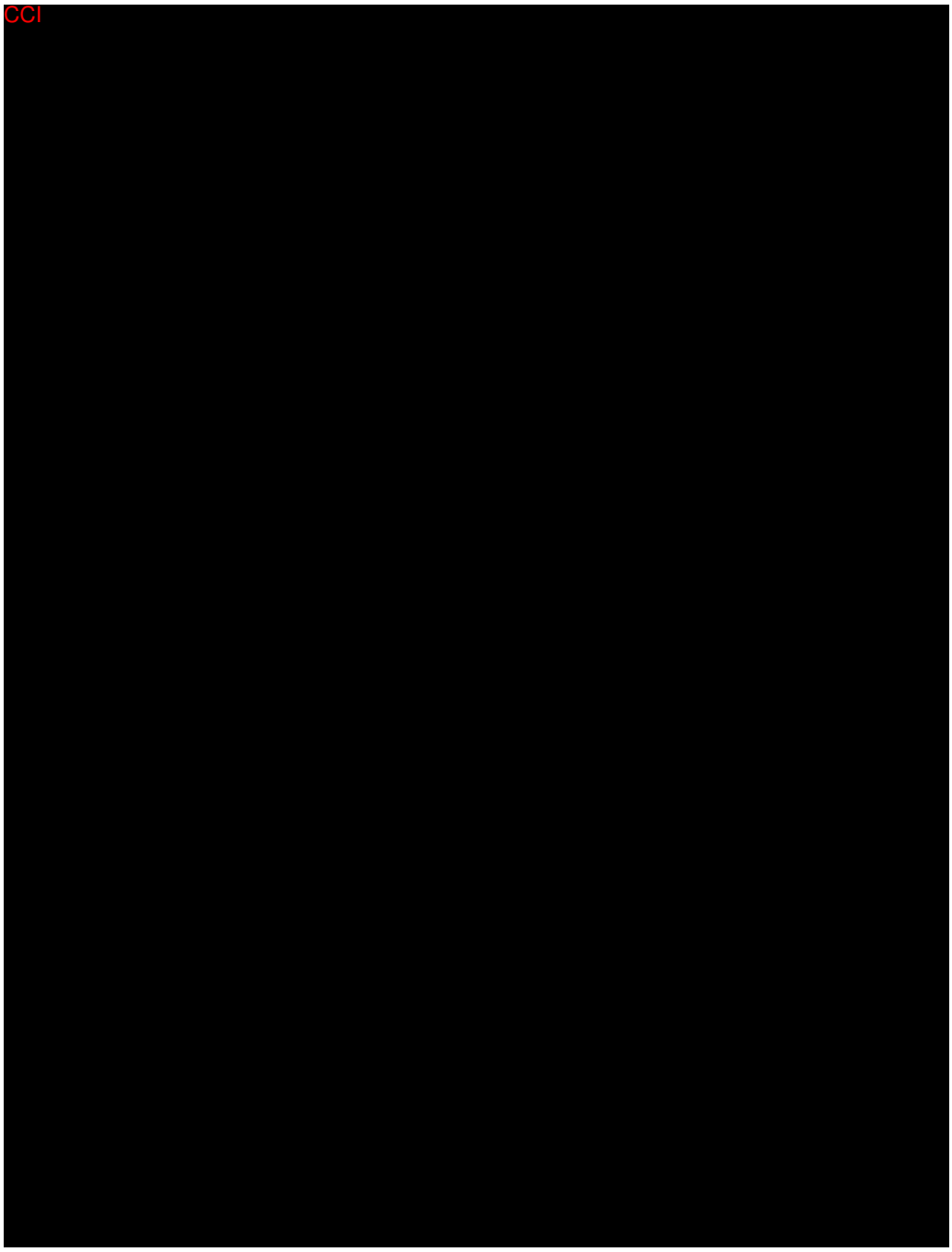
the continuous fixed covariates of baseline measurement. The nominal p-value will be provided.

For change from baseline in each of the seven ACR components, the ANCOVA model using AO data handling as described in Section 9.2.3 will be conducted as supplementary analysis, with treatment and the stratification factor of current DMARD use (yes/no) as the fixed factors and the corresponding baseline values as the covariates. Nominal p-values will be provided.

9.2.5 Handling of Multiplicity

The overall type I error rate of the primary and ranked key secondary endpoints for the two doses will be strongly controlled using a graphical multiple testing procedure.[1] Specifically, the testing will utilize the endpoint sequence of primary endpoint followed by the ranked key secondary endpoints in the order as specified in Section 9.2.3, and will begin with testing the primary endpoint using α of 0.025 for each dose. Continued testing will follow a pre-specified α transfer path which includes downstream transfer along the endpoint sequence within each dose as well as cross-dose transfer. Adjusted p-values for the primary and ranked key secondary endpoints will be provided based on the testing procedure.

The graph for the testing procedures is provided in Figure 2. In the graph, the arrows specify the α transfer paths. Once an endpoint is rejected (i.e., deemed significant) at its assigned significance level, its significance level will be transferred to subsequent endpoint(s) following the arrow(s). The numbers on the arrows denote the weights for transferring significance levels. Specifically, the weight 1 denotes 100% transfer of significance level.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9.2.6 Efficacy Subgroup Analysis

The primary efficacy endpoint will be examined in the subgroups listed in Table 6 below. Treatment difference between each upadacitinib dose and the combined placebo group will be presented with point estimate and 95% confidence interval using normal approximation. No p-value will be provided for subgroup analysis.

Table 6. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	< 65, ≥ 65 - < 75, ≥ 75 years (if sample size allows)
Sex	Male or Female
BMI	< 25 kg/m^2 or ≥ 25 kg/m^2
Race	White, Non-white
Geographic region	North America, Western Europe and Oceania, Eastern Europe, Latin-America, Asia, and Other
Duration of PsA diagnosis	≤ 5, > 5 - ≤ 10 > 10 years
Baseline hsCRP	≤ ULN or > ULN
Number of prior failed biologic DMARDs	= 1, > 1
Current use of non-biologic DMARDs	Yes or No

9.3 Long-Term Efficacy Analysis

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 44, 56 and every 12 weeks thereafter until completion of the study:

- ACR20/50/70 response rates
- Change from baseline in individual ACR components
- Change from baseline in DAS28 (CRP) and DAS28 (ESR)
- PsARC response rate
- Change from baseline in DAPSA
- Proportion of subjects achieving a clinically meaningful improvement in HAQ-DI (≥ 0.35)

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 12, 24, 36, 56 and every 12 weeks thereafter until completion of the study:

- Change from baseline in EQ-5D-5L index and VAS score
- Change from baseline in FACIT-Fatigue
- Change from baseline in SF-36
- Change from baseline in WPAI
- Change from baseline in BASDAI
- Cumulative HRU
- Change from baseline in PASDAS
- BASDAI 50 response rates
- Change from baseline in ASDAS
- Proportion of subjects with ASDAS Inactive Disease
- Proportion of subjects with ASDAS Major Improvement
- Proportion of subjects with ASDAS Clinically Important Improvement

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 12, 16, 24, 36, 56 and every 12 weeks thereafter until completion of the study:

- Change from baseline in BSA-Ps
- PASI 75/90/100 response rates
- Static Investigator Global Assessment (sIGA) of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline
- Proportion of subjects achieving Minimal Disease Activity (MDA)
- Change from baseline in LDI
- Change from baseline in LEI
- Change from baseline in SPARCC enthesitis index
- Change from baseline in dactylitis count
- Proportion of subjects with resolution of dactylitis
- Proportion of subjects with resolution of enthesitis sites included in the LEI

- 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

Assessments to evaluate long-term efficacy will be analyzed for the following measures at Week 16, 24, 36, 56 and every 12 weeks thereafter until completion of the study:

- Change from baseline in SAPS

Descriptive statistics will be provided for each randomized treatment group sequence as defined in Section 9.1.1. These include the number of observations, mean, standard deviation, 95% CI, median, minimum, and maximum for continuous endpoints; and frequencies and percentages with 95% CI using normal approximation for binary endpoints. These efficacy analyses will be based on AO data. Plot for each randomized treatment group sequence over time will be provided for key endpoints.

9.4 Efficacy Variables Definitions and Conventions

9.4.1 ACR Criteria

ACR criteria are a commonly used standard criteria set mentioned in the FDA industry guidance to evaluate the effectiveness of investigational drug in reduction of disease activity. It is a composite measurement calculated based on the improvement over a set of core measurements.

ACR20 is defined as at least 20% improvement (compared to baseline values) in tender and swollen joint counts and at least 20% improvement in 3 of the remaining 5 core set measures (subject assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant hsCRP).

ACR50 and ACR70 are similarly defined with at least 50% and 70% improvement, respectively.

A subject will be classified as an ACR20 (ACR50, ACR70) responder, if the following conditions are met:

1. ≥ 20% (50%, 70%) improvement from baseline in tender joint count (TJC68) and
2. ≥ 20% (50%, 70%) improvement from baseline in swollen joint count (SJC66) and
3. ≥ 20% (50%, 70%) improvement from baseline in at least 3 of the following 5:
    - patient's assessment of pain
    - patient's global assessment of disease activity (PtGA)
    - physician's global assessment of disease activity (PGA)
    - patient's self-assessment of physical function (i.e., measured by Health Assessment Questionnaire HAQ-DI score)
    - Acute-phase reactant value high-sensitivity CRP (hsCRP)

Seven components are included in the ACR response criteria. Missing values for a component can occur due to data collection issues for a particular form, a missed visit or dropout from the study. Depending on the pattern of the missing components, ACR responses may be or may not be determined for a visit date using (partially) observed values only. In the case when ACR responses cannot be determined for any visit date within a visit window, partially observed data from different visit dates within the same visit window can be combined to determine ACR responses for the visit window.

To maximize the utilization of observed information at certain visits and be scientifically as robust as possible, the principle to calculate ACR response is to minimize imputation whenever possible. "As Observed" ACR response will be calculated first based on a derived visit window instead of the nominal visit identifier (e.g., Week 6 visit) collected from the CRF.

To calculate "as observed" ACR responses:

Identify the observed component 20% improvement indicator (0/1/missing), 1 means achieving ≥ 20% improvement from baseline and 0 means < 20% improvement from baseline.

ACR20 = 0 if TJC indicator = 0 OR SJC indicator = 0 OR at least 3 out of 5 components improvement indicators = 0;

ACR20 = 1 if TJC indicator = 1 AND SJC indicator = 1 AND at least 3 out of 5 components improvement indicators = 1

For all other cases, "as observed" ACR20 = missing since ACR20 cannot be determined.

The following table illustrates examples for observed ACR calculations.

Example	TJC 68	SJC 66	Component 1	Component 2	Component 3	Component 4	Component 5	ACR20-Response?
A	1	1	1	1	1	.	.	Yes
B	1	0	1	1	1	1	1	No
C	.	0	.	.	.	.	.	No
D	1	.	1	1	1	1	1	.
E	1	1	0	0	0	1	1	No
F	.	.	0	0	0	.	.	No
G	1	1	1	1	0	0	.	.

Legend: 1 = ≥ 20% improved compared to baseline; 0 = < 20% improved compared to baseline; "." Missing

Derived visit windowing Rule for ACR Response Calculation:

To identify the component value in a visit window:

ACR component values will first be determined at each date within a visit window.

ACR component values at each date will be combined to determine the "as observed" ACR composite score at each date in each window.

After this calculation, if multiple non-missing ACR composite scores are available within a given visit window, the non-missing ACR composite score closest to the target day will be used. If two composite scores have the same distance from the target day, the later one will be used. The corresponding date will be used as the "as observed" ACR response date in the derived efficacy dataset.

If a non-missing ACR composite score is not available for any day within a given visit window, the windowed component values for that visit will be used to calculate the ACR composite score for that visit window (component value windowing follow the same rules as in steps described above). Date of TJC will be used as the "as observed" ACR date in the derived efficacy dataset.

The following rules are applied for the NRI imputation for the ACR responses.

Non-Responder Imputation (NRI):

- Step 1: all missing components will be imputed using LOCF, and then the ACR composite score can be calculated
- Step 2: if the ACR composite score cannot be determined by step 1, the ACR composite score will be imputed as 0. In addition, subjects who prematurely discontinue from the study drug will be considered as non-responders (ACR = 0) for all subsequent visits after the discontinuation date.

9.4.2 Joint Evaluation

Anatomical joints are evaluated for swelling and tenderness at every study visit. The 34 anatomical joints in Table 7 are assessed in this study for both the left and right side of the body.

Table 7. Anatomical Joints Assessed for Calculation of Tender and Swollen Joint Counts (TJC68 and SJC66)

Temporomandibular	Sternoclavicular	Acromio-clavicular	Shoulder
Elbow	Wrist	Metacarpophalangeal I	Metacarpophalangeal II
Metacarpophalangeal III	Metacarpophalangeal IV	Metacarpophalangeal V	Thumb Interphalangeal
Proximal Interphalangeal II	Proximal Interphalangeal III	Proximal Interphalangeal IV	Proximal Interphalangeal V
Distal Interphalangeal II	Distal Interphalangeal III	Distal Interphalangeal IV	Distal Interphalangeal V
Hip[a]	Knee	Ankle	Tarsus
Metatarsophalangeal I	Metatarsophalangeal II	Metatarsophalangeal III	Metatarsophalangeal IV
Metatarsophalangeal V	Great Toe/Hallux	Interphalangeal II	Interphalangeal III
Interphalangeal IV	Interphalangeal V		

a. Hip joints are not assessed for swelling.

At each study visit, a joint evaluator will assess whether a particular joint was "tender or painful" where presence of tenderness is scored as "1" and the absence of tenderness is scored as "0," provided the joint was not replaced ("9") or could not be assessed ("NA") due to other reasons (e.g., post-corticosteroid joint injection). The total tender joint count (TJC68), which is based on 68 joints, will be derived as the sum of all "1s" and proportional extrapolation will be used to impute joint counts for the joints that are replaced or not assessed. A similar method will be followed for the derivation of total swollen joint count (SJC66), which is based on 66 joints as the hip joints are excluded. Thus, the range for TJC68 will be 0 to 68 and 0 to 66 for SJC66.

9.4.3 Patient's Global Assessment of Disease Activity Numeric Rating Scale (NRS)

The subject will assess his/her disease activity using the Patient's Global Assessment of Disease NRS. The range is 0 to 10 with no activity being indicated by 0 and severe activity by 10.

9.4.4 Physician's Global Assessment of Disease Activity Numeric Rating Scale (NRS)

The physician will assess Patient's disease activity at the time of visit using the Physician's Global Assessment of Disease NRS. The range is 0 to 10 with no activity being indicated by 0 and severe activity by 10.

9.4.5 Patient's Assessment of Pain Numeric Rating Sale (NRS)

The subject will assess his/her pain using the Patient's Global Assessment Pain NRS. The range is 0 to 10 with no activity being indicated by 0 and severe activity by 10.

9.4.6 Disease Activity Score (DAS28)

DAS28 (CRP) and DAS28 (ESR) are composite indices to assess disease activity in PsA using hsCRP or ESR measurement, respectively. The DAS28 provides a score between 0 and 10, indicating arthritis disease activity at the time of measurement.

DAS28 (CRP) and DAS28 (ESR) is calculated based on Tender Joint Count, Swollen Joint Count, PtGA of Disease Activity (0-100), and hsCRP (in mg/L) or ESR (mm/hr).

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

$$\text{DAS28 (ESR)} = 0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \ln(\text{ESR}^{\#}) + 0.014 \times \text{PtGA}^{\text{»}}$$

where √ is square root and ln is natural log.

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

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

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

\# ESR refers to the Erythrocyte sedimentation rate. ESR unit in the DAS28 (ESR) equation is expressed as mm/hr.

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

Table 8. Anatomical Joints for DAS28 (CRP) Calculation

Shoulder	Elbow	Wrist	Thumb Interphalangeal
Metacarpophalangeal I	Metacarpophalangeal II	Metacarpophalangeal III	Metacarpophalangeal IV
Metacarpophalangeal V	Proximal Interphalangeal II	Proximal Interphalangeal III	Proximal Interphalangeal IV
Proximal Interphalangeal V	Knee		

As PtGA of Disease Activity is collected with the scale of 0-10 NRS, the variable needs to be multiplied by 10 before being used the DAS28 formula.

To calculate observed DAS28 scores, the observed component value will be calculated first. Then the components will be included in the calculation per the DAS formula selected. If any observed component is missing in a window, then the observed DAS28 score will be missing.

9.4.7 Disease Activity in Psoriatic Arthritis (DAPSA) Score

DAPSA is a continuous endpoint that measures the disease activity in psoriatic arthritis. DAPSA consists of five components: Tender Joint Count 68, Swollen Joint Count 66, Patient's Assessment of Pain (0-10 NRS), PtGA of Disease Activity (0-10 NRS), and hsCRP (in mg/dL).

DAPSA = SJC66 + TJC68 + Pt pain (0-10 NRS) + PtGA (0-10 NRS) + hsCRP (in mg/dL)

To calculate observed DAPSA scores, the observed component value will be calculated first. Then the components will be included in the calculation per the DAPSA formula. If any observed component is missing in a window, then the observed DAPSA score will be missing.

9.4.8 PsA Disease Activity Score (PASDAS)

PASDAS is a continuous scale of combined joint, dactylitis and enthesitis assessments, physician and patient global assessments for arthritis, SF36-PCS, and hsCRP measurements.

PASDAS = (((0.18 √(PGA)) + 0.159 √(PtGA) - 0.253 √(SF36-PCS) + 0.101 ln (SJC66 + 1) + 0.048 ln (TJC68 + 1) + 0.23 ln (Leeds Enthesitis Index+ 1) + 0.37 ln (Tender Dactylitis Count + 1) + 0.102 ln (hsCRP + 1) + 2) * 1.5,

where √ is square root and ln is natural log. PtGA is on the scale of 0 – 100 and PGA is on the scale of 0 – 100. As PtGA and PGA are collected with the scale of 0-10 NRS, their values need to be multiplied by 10 before being used in the PASDAS formula.

SF36-PCS is the physical component scale in SF36 instrument. The unit for hsCRP is mg/L.

The tender dactylitis count is based on the dactylitis assessment. The count is calculated by summing the digits with a "presence of tenderness" score = 1.

The Leeds Enthesitis Index (LEI) evaluates enthesitis at 6 most commonly involved entheseal sites, as indicated in the table below. The LEI is calculated by taking the sum of the scores from the 6 sites. The LEI ranges from 0 to 6.

		Tenderness in Left			Tenderness in Right		
		YES = 1	NO = 0	Not Assessed = NA	YES = 1	NO = 0	Not Assessed = NA
1	Lateral epicondyle						
2	Achilles tendon insertion						
3	Medial femoral condyle						

To calculate observed PASDAS scores, the observed component value will be calculated first. Then the components will be included in the calculation per the PASDAS formula. If any observed component is missing in a window, then the observed PASDAS score will be missing.

9.4.9 Disability Index of Health Assessment Questionnaire (HAQ-DI)

HAQ-DI is a self-reported patient outcome measurement. It is calculated as the mean of the scores from 8 following categories with a range 0 – 3: Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. Higher scores reflect greater disability.

The maximum score for all the questions in each category is considered as the score for the category. The HAQ-DI takes into account the subject's use of aids or devices or assistance in the scoring algorithm for a disability category. For each category there is an AIDS OR DEVICES companion variable that is used to record the type of assistance, if any, a subject uses for his/her usual activities. If aids or devices and/or assistance from another person are checked for a category, the score for this category is set to 2 (much difficulty), if the original score is 0 (no difficulty) or 1 (some difficulty). The HAQ-DI is then calculated by summing the adjusted categories scores and dividing by the number of categories answered. The HAQ-DI cannot be calculated if the subject does not have scores for at least 6 categories.

9.4.10 Static Investigator Global Assessment of Psoriasis (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 assessment, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit. A lower score indicates less severe psoriasis (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe).

A binary clinical endpoint based on sIGA is considered in this study. It is the proportion of subjects achieving a sIGA score of 0 or 1 and at least a 2-point improvement from baseline. This endpoint is calculated among the subjects with baseline sIGA score ≥ 2.

9.4.11 Psoriasis Area Severity Index (PASI)

Psoriasis Area Severity Index (PASI) has four anatomic sites – head, upper extremities, trunk, and lower extremities – which are assessed for erythema, induration and desquamation using a 5-point scale:

- 0 = no symptoms
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

Based on the extent of lesions in a given anatomic site, the area affected is assigned a numerical value:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% – 29%
- 3 = 30% – 49%
- 4 = 50% – 69%
- 5 = 70% – 89%
- 6 = 90% – 100%

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:

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

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.

If an item is missing, PASI is not scored.

PASI 75 (PASI 50, PASI 90, PASI 100) response is achieved if there is at least a 75% (50%, 90%, 100%) reduction in PASI score (≥ PASI 75/50/90/100 response) at a visit relative to the Baseline PASI score.

PASI is summarized in subjects with ≥ 3% BSA (Body Surface Area) psoriasis involvement at baseline.

9.4.12 Minimum Disease Activity for PsA

A patient is classified as in MDA when 5 of the following 7 criteria are met:

- TJC68 ≤ 1
- SJC66 ≤ 1
- PASI ≤ 1 or BSA-Ps ≤ 3%
- Patient's assessment of pain ≤ 1.5 (0 - 10 NRS)
- Patient's Global Assessment of disease activity ≤ 2 (0 - 10 NRS)
- HAQ-DI score ≤ 0.5
- Leeds Enthesitis Index ≤ 1

MDA response can be determined if at least 5 of the 7 criteria are met (responder), or if at least 3 of the 7 criteria are not met (non-responder). Selection of multiple MDA responses within one visit window follows the same rules as ACR. Missing values for each component can occur due to data collection issues for a particular form, a missed visit or dropout from the study. Depending on the pattern of the missing components, MDA responses may be or may not be determined for a visit date using (partially) observed values only. In the case when MDA responses cannot be determined for any

visit date within a visit window, partially observed data from different visit dates within the visit window can be combined to determine MDA responses for the visit window.

9.4.13 Self-Assessment of Psoriasis Symptoms (SAPS)

The Self-Assessment of Psoriasis Symptoms (SAPS) contains 11 symptom-focused items. Each item is scored from 0 to 10, with 0 being least severe and 10 being most severe. The total score is generated by summing the 11 items. The total score ranges from 0 to 110.

9.4.14 Leeds Dactylitis Index (LDI) and Dactylitis Count

The Leeds Dactylitis Index (LDI) is a score based on finger circumference and tenderness, assessed and summed across all dactylitic digits. The presence of dactylitis digit is defined as at least one affected AND tender digit with circumference increase over reference digit ≥ 10%. For each of 20 digits of a subject, a digit final score needs to be calculated first. For an unaffected digit, the digit final score is set to be 0. For an affected digit, the digit final score is calculated as (A/B-1)*100*C if A/B ≥ 1.1, and digit finals score = 0 if A/B < 1.1, where A denotes the circumference of the digit, B the reference circumference, and C the tenderness score. The reference circumference can be either the circumference of the unaffected contralateral digit if available, or from a reference table if otherwise. LDI is the sum of the digit final scores over all 20 digits.

The dactylitis count will be calculated as the number of digits (hands and feet) with presence of dactylitis. The count ranges from 0 to 20.

The proportion of subjects with resolution of dactylitis is defined as the proportion of subjects with LDI = 0.

9.4.15 Leeds and SPARCC Enthesitis Indices and Total Enthesitis Count

For the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index 16 sites are evaluated as indicated in rows 1 – 8 in the table below. Tenderness on examination is recorded as either present (coded as 1), absent (coded as 0), or not assessed

for each site. The SPARCC enthesitis index is calculated by taking the sum of the scores from the 16 sites. The SPARCC score ranges from 0 to 16.

The Leeds Enthesitis Index evaluates enthesitis at the 6 entheseal sites indicated in rows 2, 7 and 9 in the table below. Tenderness on examination is recorded as either present (coded as 1), absent (coded as 0), or not assessed for each of the 6 sites. The LEI is calculated by taking the sum of the scores from the 6 sites. The LEI ranges from 0 to 6.

The total enthesitis count is calculated by taking the sum of the tenderness scores from all 18 sites in the table below.

The proportion of subjects with resolution of enthesitis sites included in the LEI is defined as the proportion of subjects with LEI = 0; the proportion with resolution of the SPARCC Enthesitis Index and of the total enthesitis count are similarly defined.

		Tenderness in Left			Tenderness in Right		
		Present = 1	Absent = 0	Not Assessed = NA	Present = 1	Absent = 0	Not Assessed = NA
1	Medial epicondyle						
2	Lateral epicondyle						
3	Supraspinatus insertion into the greater tuberosity of humerus						
4	Greater trochanter						
5	Quadriceps insertion into superior border of patella						
6	Patellar ligament insertion into inferior pole of patella or tibial tubercle						
7	Achilles tendon insertion into calcaneum						
8	Plantar fascia insertion into calcaneum						
9	Medial femoral condyle						

9.4.16 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 by the physician is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved.

9.4.17 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Morning Stiffness Score

The BASDAI is composed of 6 items investigating 5 domains (fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness), with 1 item for each of the first four domains and 2 items for the last domain (morning stiffness). Each item is scored on a 0-10 NRS. A lower score indicates less disease activity.

Scoring of the BASDAI is as follows:

1. Measure each item of the BASDAI in NRS (out of a total of 10)
2. BASDAI Score = 0.2*(Item1 + Item2 + Item3 + Item4 + 0.5*Item5 + 0.5* Item6)

The BASDAI Score ranges from 0 – 10. If one of the 5 items (Questions 1 – Question 4, inflammation) is missing, then the score is the mean of the 4 non-missing items (total of 4 non-missing items divided by 4). If more than 1 of the 5 items is missing, then the BASDAI score is missing.

Note: Question 5 and Question 6 jointly constitute Item 5 (inflammation). If both Questions 5 and 6 are missing, and questions 1 through 4 are non-missing, then only one item will be considered missing. The BASDAI score can still be calculated as the mean of Questions 1 – 4. However, if, for example, both Question 6 and Question 1 are missing, then 2 items will be considered missing, as the inflammation calculation would be incomplete. The BASDAI score would then be considered missing in this case.

The Morning Stiffness Score is the average of BASDAI questions 5 and 6 and it ranges from 0 – 10.

9.4.18 Modified Psoriatic Arthritis Response Criteria (PsARC)

The modified PsARC is a PsA-specific composite responder index. To achieve response, a subject must achieve 2 of the following 4 items, one of which has to be a Tender Joint Count 68 or Swollen Joint Count 66, and no worsening of any measure:

- ≥ 30% improvement in TJC68
- ≥ 30% improvement in SJC66
- Improvement in PtGA of Disease Activity NRS
- Improvement in PGA of Disease Activity NRS

Four components are included in the PsARC criteria. Missing values for each component can occur due to data collection issues for a particular form, a missed visit or dropout from the study. In the case when PsARC responses cannot be determined for any visit date within a visit window, partially observed data from different visit dates within the visit window can be combined to determine PsARC responses for the visit window.

9.4.19 Ankylosing Spondylitis Disease Activity Score (ASDAS)

Parameters used for the calculation of ASDAS:

1. Patient's assessment of total back pain (BASDAI Question 2)
2. PtGA of disease activity (0-10 NRS)
3. Peripheral pain/swelling (BASDAI Question 3)
4. Duration of morning stiffness (BASDAI Question 6)
5. High-sensitivity C-reactive protein (hs-CRP) in mg/L.

Calculation of ASDAS:

$ASDAS_{hs\text{-}CRP}$ = 0.121 × total back pain + 0.110 × PtGA + 0.073 × peripheral pain/swelling + 0.058 × duration of morning stiffness + 0.579 × Ln(hs-CRP+1).

To calculate observed ASDAS scores, the observed component value will be calculated first. Then the components will be included in the calculation per the ASDAS formula. If any observed component is missing in a window, then the observed ASDAS score will be missing.

ASDAS score is categorized by the following ASDAS Disease Activity States:

- ASDAS Inactive Disease: ASDAS < 1.3
- ASDAS Moderate Disease: 1.3 ≤ ASDAS < 2.1
- ASDAS High Disease: 2.1 ≤ ASDAS ≤ 3.5
- ASDAS Very High Disease: ASDAS > 3.5

ASDAS Response categories are defined as follows:

- ASDAS Major Improvement (a change from baseline ≤ –2.000)
- ASDAS Clinically Important Improvement (a change from baseline ≤ –1.100)

9.4.20 FACIT-Fatigue Questionnaire (FACIT-F)

The FACIT Fatigue Questionnaire is a 13-item tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point scale (4 = not at all fatigued to 0 = very much fatigued). The Fatigue scale ranges from 0 to 52, with higher scores indicating less fatigue.

Item score for each item is calculated by either subtracting from 4 or adding 0 depending on whether it is a reversal item or not. FACIT Fatigue Scale is then calculated by adding up all item scores, multiplying by 13 and dividing by the number of items answered. If less than 7 items are answered, the scale will not be computed.

9.4.21 EuroQoL-5D (EQ-5D-5L)

EQ-5D measures 5 dimensions of health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels per dimension (no problems, slight problems, moderate problems, severe problems, and extreme problems corresponding to Level 1 to Level 5 respectively) and includes the EQ Visual Analogue Scale (EQ VAS). The 5 dimensions of health status are converted into a single index value. The change from baseline of the index value and the EQ VAS will be analyzed and reported. UK scoring algorithm will be used.

9.4.22 Form SF-36v2

The 36-Item Short Form, Version 2 (SF-36v2) health survey consists of 36 general health questions. It has 2 components: physical and mental. For each component, a transformed summary score is calculated using 8 sub domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

The coding and scoring for the SF-36 will use the software provided by QualityMetrics.

9.4.23 Work Productivity and Activity Impairment Questionnaire Psoriatic Arthritis (WPAI)

The Work Productivity and Activity Impairment Questionnaire: Psoriatic Arthritis, V2.0 (WPAI) was developed to measure the effect of overall health and specific symptoms on productivity at work and outside of work. It consists of 6 questions. A lower WPAI score indicates an improvement. The WPAI is collected at the designated study visits listed in the protocol. The WPAI coding and scoring methods are described in the following:

The 6 measures will be derived based on the responses from the 6 questions. The 4 main impairment scores (S1 to S4) are expressed as *percent impairment* based on the 6 questions.

Scores:

S0. Employment: defined below in missing data handling conventions

S1. Absenteeism: Percent work time missed due to PsA:

$$100 \times \left[\frac{Q2}{Q2 + Q4} \right]$$

S2. Presenteeism: Percent impairment while working due to PsA:

$$100\times\left[\frac{Q5}{10}\right]$$

S3. Percent overall work impairment due to PsA:

$$100\times\left[\frac{Q2}{Q2+Q4}+\left\{1-\frac{Q2}{Q2+Q4}\right\}\times\frac{Q5}{10}\right]$$

S4. Percent activity impairment due to PsA:

$$100\times\left[\frac{Q6}{10}\right]$$

S5. Did subject miss work (defined below). This is needed to derive the proportion of subjects who missed work.

Missing Data Handling Conventions

When calculating the WPAI: PsA scores, the following computational notes should be followed.

- Define Employment as a binary YES or NO variable where YES corresponds to "Employed" and NO corresponds to "Not Employed."
  - A subject will be considered "employed" at a given visit if Q1 = YES or Q2 > 0 or Q4 > 0.
  - A subject will be considered "unemployed" at a given visit if Q1 = NO and no positive hours recorded under Q2 and Q4 (i.e., if Q1 = NO AND Q2 ≤ 0 AND Q4 ≤ 0, then UNEMPLOYED).
  - Employment status for a subject will be considered "missing" at a given visit if Q1 = missing and no positive hours recorded under Q2 and Q4.

- If a subject is "unemployed" or employment status is "missing," then S1, S2, and S3 will be set to "missing."
- If Q2 = 0 and Q4 = 0 or missing then Q2/(Q2 + Q4) = missing (i.e., S1 = missing).
- If Q2 = 0 and Q4 = 0, then set S3 to missing.
- If Q2 is missing or Q4 is missing, then set S1 and S3 to missing.
- If Q4 = missing, then DO NOT set Q5 = missing.
- If Q5 is missing, then apply the following rules:
  - If Q2 > 0, Q4 = 0, and Q5 = missing, then S3 = 100%.
  - If Q2 = 0, Q4 > 0, and Q5 = missing, then S3 is missing.
  - If Q2 > 0, Q4 > 0, and Q5 = missing, then S3 is missing.
- Determine if a subject missed work (based on Q2) in order to analyze the proportion of subjects who missed work:
  - Create a binary (yes or no) "missed work" variable.
  - A subject will be considered as yes to missed work if Q2 is greater than 0.
  - If Q2 = missing, then MISSED WORK = missing.
  - If Q2 > 0, then MISSED WORK = "yes."
  - If Q2 = 0, then MISSED WORK = "no."

Therefore, the proportion of subjects who missed work will be counted based on the number of subjects with MISSED WORK = YES.

9.4.24 Health Resource Utilization (HRU) Questionnaire

The HRU questionnaire contains three questions regarding health care utilization in the following categories: unscheduled health care professional visits, emergency room visits, and hospital admissions. The data gathered from the HRU questionnaire will be used to calculate the individual cumulative number of utilizations per unit of time (e.g., subject-year) under observation in each variable (i.e., the number of unscheduled PsA-related health care professional visits, the number of emergency room visits, the number of hospital admissions and the total number of days in hospital) as follows:

- Time under observation for a subject will be defined as "date of last visit with non-missing HRU – date of baseline visit."
- The number of utilizations after baseline will be summed up for each subject.

To determine cumulative HRU over all subjects, the ratio of the total number of utilizations (i.e., over all subjects) and the total time under observation (i.e., over all subjects) will be calculated across all subjects in each treatment group. HRU will be analyzed as observed only.

10.0 Safety Analysis

10.1 General Considerations

Safety analyses will be carried out using the Safety Analysis Set by "as treated" treatment groups. There are two sets of planned safety analysis: safety analysis through Week 24, and long-term safety analysis.

Safety Analysis Through Week 24

Standard safety analyses by the "as treated" treatment groups of upadacitinib 15 mg QD, upadacitinib 30 mg QD, and the combined placebo group will be performed on safety data up to Week 24. No protocol-defined treatment switching will occur prior to this time point.

The standard safety analyses will include reporting of adverse events (AEs), laboratory, and vital signs measurements. Frequency tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be provided by treatment groups. All continuous laboratory parameters and vital signs variables at each visit will be summarized by treatment groups. Frequency tables of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values will be provided by treatment groups. Missing safety data will not be imputed. Treatment comparations of upadacitinib versus placebo will be

provided for key safety endpoints including overview of AE, overview of AE of special interest, change from baseline in selected laboratory parameters and potentially clinically significant laboratory values. Treatment difference and corresponding 95% CI will be provided.

Long-Term Safety Analysis

Long-term safety analyses that account for protocol-defined treatment switching include reporting of AE rate adjusted by cumulative exposure, descriptive summary in laboratory parameters and vital sign variables by visit, and rate of potentially clinically significant laboratory and vital signs values. The treatment-emergent adverse event (TEAE) rate per 100 patient-years of exposure will be presented by actual treatment received at the time of AE (as described in Section 10.2.2). Listing of subjects with TEAEs by SOC and PT will be provided. Summary statistics for laboratory parameters and vital signs variables at each visit will be presented by "as treated" treatment group sequences defined below. Frequency tables and listings of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values will be provided by actual treatment received at the time of event. Missing safety data will not be imputed.

"As treated" treatment group sequences are defined as follows:

1. Placebo → Upadacitinib 15 mg QD
2. Placebo → Upadacitinib 30 mg QD
3. Upadacitinib 15 mg QD
4. Upadacitinib 30 mg QD

10.2 Analysis of Adverse Events

A treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is after the first dose of study drug, and no more than 30 days after the last dose of study drug.

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

Adverse event data will be presented by SOCs and PTs using MedDRA Version 19.1 or most up to date version, which will be sorted in alphabetical order by SOC and PT.

10.2.1 Analysis of Adverse Events Prior to Protocol-Defined Treatment Switching

10.2.1.1 Adverse Events Overview

The number and percentage of subjects experiencing TEAEs will be summarized by treatment groups for the following AE categories.

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs with a reasonable possibility of being related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death
- Deaths (includes all deaths - treatment-emergent and non-treatment-emergent)

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

10.2.1.2 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing adverse events will be tabulated by SOC and PT by treatment groups. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The following summaries of adverse events will be generated:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs with a reasonable possibility of being related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

Subjects reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

10.2.1.3 TEAEs by Maximum Severity

TEAEs will also be summarized by maximum severity by treatment groups. If a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest CTCAE grade; in this case, the subject will be counted under the highest CTCAE grade for the term in question.

10.2.1.4 TEAEs by Relationship

TEAEs will also be summarized by relationship to upadacitinib and placebo, as assessed by the investigator, by treatment groups. If a subject has a TEAE with an unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same TEAE with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

10.2.1.5 Frequent (≥ 2%) Adverse Events and Reasonably Possibly Related Adverse Events by System Organ Class and Preferred Term

TEAEs and reasonably possibly related AEs occurring for more than 2% of the subjects in any of the treatment groups will be summarized by SOC and PT separately.

10.2.1.6 Adverse Events of Special Interest

The Adverse Events of Special Interest (AESI) categories will be summarized and presented by treatment groups in overview as well as using SOC and PT. The AESI categories will be identified by the following search criteria per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs) in Table 9 below. Adjudicated cardiovascular events will be summarized and presented by treatment group using the CAC adjudicated categories.

Table 9. AESI for Upadacitinib with SMQs/CMQs/PTs Searches

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Serious Infections	CMQ		"Infections" – Subset for SAEs
Opportunistic Infection excluding Tuberculosis and Herpes Zoster	CMQ		"Opportunistic Infection"
Possible Malignancy	SMQ	Narrow	"Malignancies"
Malignancy	SMQ		"Malignant tumours"
Non-Melanoma Skin Cancer (NMSC)	SMQ	Narrow	Skin Malignant tumours (Narrow SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			"Malignant tumours" SMQ removing NMSC output
Lymphoma	SMQ		"Malignant Lymphomas"
Hepatic Disorder	SMQ	Narrow	"Drug Related Hepatic Disorders"
Gastrointestinal Perforations	Output from Medical Review of Events Identified by the "Gastrointestinal Perforation" SMQ Narrow Search		
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity – Lymphopenia"
Herpes Zoster	CMQ		"Herpes Zoster"
Creatine Phosphokinase (CPK) Elevation	PT		Search only for the PT of "Blood creatine phosphokinase increased"
Renal Dysfunction	SMQ	Narrow	"Acute Renal Failure"
Active Tuberculosis	CMQ		"Active Tuberculosis"

Table 9. AESI for Upadacitinib with SMQs/CMQs/PTs Searches (Continued)

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Adjudicated Cardiovascular Events	Output from CAC		
MACE*			
Cardiovascular Death			
Non-fatal Myocardial Infarction			
Non-fatal Stroke			
Other Adjudicated Cardiovascular Events			
Undetermined/Unknown Cause of Deaths			
Adjudicated Thrombotic Events	Output from CAC		
VTE**			
Deep Vein Thrombosis			
Pulmonary Embolism			
Other Venous Thrombosis			
Arterial Thromboembolic Events (non-cardiac, non-neurologic)			

CAC = Cardiovascular Adjudication Committee; CMQ = company MedDRA query; PT = preferred term; SMQ = standard MedDRA query

* MACE; Major Adverse Cardiovascular Events, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

** VTE: Venous thromboembolic events, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE) (fatal and non-fatal).

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

10.2.2 Analysis of Long-Term Adverse Event Rates

Long-term adverse event rates will be analyzed using event rates adjusted by cumulative exposure and will be based on the actual treatment received at the time of AE occurrence. The detailed treatment groups are defined as follows.

1. Any upadacitinib 15 mg QD

   This includes AEs which occurred under upadacitinib 15 mg QD exposure from subjects starting on upadacitinib 15 mg QD and subjects switching from placebo to upadacitinib 15 mg QD.

2. Any upadacitinib 30 mg QD

   This includes AEs which occurred under upadacitinib 30 mg QD exposure from subjects starting on upadacitinib 30 mg QD and subjects switching form placebo to upadacitinib 30 mg QD.

Exposure-Adjusted Event Rate (EAER)

To adjust for potentially different follow-up time between treatment groups, EAER will be provided. For the purpose of event rate calculation, the numerator will be the total number of AEs reported for the event (i.e., a subject can contribute more than one event to the numerator) and the denominator will be the total exposure time among subjects under the treatment group. The number of AEs reported (numerator), the total number of years of study drug exposure (denominator), and the exposure-adjusted AE event rate per 100 patient-years calculated as ([numerator/denominator]) • 100 will be presented for each treatment group. The EAER will be the main approach to evaluate AEs in the long-term analysis.

The exposure adjusted incidence rate (censored at the time of first event) may be conducted for selected AESI endpoints as appropriate for long-term analysis.

10.2.2.1 Overview of Adverse Events Rates per 100 Patient-Years of Study Drug Exposure

An overview of AEs per 100 patient-years of study exposure will be presented by treatment group for the following AE categories.

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs with a reasonable possibility of being related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death
- Deaths (includes all deaths - treatment-emergent and non-treatment-emergent)

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

10.2.2.2 Adverse Events Rates per 100 Patient-Years of Study Drug Exposure by SOC and PT

For each treatment group, the TEAE rate per 100 patient-years of exposure will be calculated overall, for each SOC and each PT, for each of the following AE categories:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs with a reasonable possibility of being related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

10.2.2.3 Adverse Events of Special Interest Rates per 100 Patient-Years of Study Drug Exposure by SOC and PT

The Adverse Events of Special Interest (AESI) categories will be summarized and presented for each treatment group in overview as well as using SOC and MedDRA PT, for each of the AESI listed in Section 10.2.1.6. The AESI categories will be identified per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs). Adjudicated cardiovascular events will be summarized and presented by treatment group using the CAC adjudicated categories.

10.2.2.4 Listing of Serious Adverse Events (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All serious adverse events (SAEs), deaths, and adverse events leading to discontinuation of study drug will be listed.

10.3 Analysis of Laboratory Data

10.3.1 Variables and Units

All laboratory parameters to be collected in this study are listed below. Laboratory parameters will be reported using the standard international (SI) units.

Table 10. List of Laboratory Variables

Laboratory Variables
Hematology
White Blood Cell (WBC) Count
Red Blood Cell (RBC) Count
Hemoglobin
Hematocrit
Platelet count
Neutrophils
Basophils
Eosinophils
Lymphocytes
Monocytes
Bands
Chemistry
Total Bilirubin
Alkaline Phosphatase (ALP)
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total Protein
Albumin
Glucose
Triglycerides
Blood Urea Nitrogen (BUN)
Creatinine
Sodium
Potassium
Calcium
Inorganic Phosphorus
Creatine Phosphokinase (CPK)
Chloride
Bicarbonate

Table 10. List of Laboratory Variables (Continued)

Laboratory Variables
Chemistry (Continued)
Cholesterol
LDL cholesterol
HDL cholesterol
LDL/HDL ratio
Cholesterol/HDL ratio
Urinalysis
Specific Gravity
pH
Protein
Glucose
Ketones
Blood
Microscopic Examination (if needed)
Urobilinogen
Bilirubin
Leukocytes
Nitrites
Other
hs-CRP
ESR

10.3.2 Analysis of Laboratory Data Through Week 24

The laboratory data will be summarized by the treatment groups (upadacitinib 15 mg QD, upadacitinib 30 mg QD, and the combined placebo group).

10.3.2.1 Assessment of Clinical Laboratory Variables

Analyses of hematology, chemistry, and urinalysis variables which are measured longitudinally will be performed by visits and by treatment groups. For analysis at each

visit, the following summary statistics of visit values will be presented for each treatment group: sample size, mean, standard deviation, minimum, median, and maximum.

An ANOVA model with treatment as a factor will be used to compare change from baseline between different treatment groups for selected laboratory parameters. Mean difference from placebo and associated 95% CIs will be presented. The analysis applies to the following laboratory parameters of clinical interest: hemoglobin, platelets, lymphocytes, neutrophils, creatinine, ALT, AST, creatine phosphokinase (CPK), LDL, HDL, total cholesterol/HDL-cholesterol, LDL-cholesterol/HDL-cholesterol, and total cholesterol.

10.3.2.2 Assessment of Shift from Baseline in Clinical Laboratory Variables

The baseline and post-baseline laboratory observations will be categorized as Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 and shifts from baseline grade to worst on-therapy grade will be summarized. Toxicity grading scale is based on National Cancer Institute Common Toxicity Criteria (NCI CTC) AE version 5.0. For the parameters with no quantitative grading available in version 5.0, CTCAE version 4.03 will be used. Shift tables from Baseline according to the grades will be provided for laboratory variables.

For LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides, the following categories according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines will be used.

- LDL cholesterol (< 3.36, ≥ 3.36 and < 4.14, ≥ 4.14 mmol/L)
- HDL cholesterol (< 1.03, ≥ 1.03 mmol/L)
- Total cholesterol (< 5.17, ≥ 5.17 and < 6.21, ≥ 6.21 mmol/L)
- Triglycerides (< 1.69, ≥ 1.69 and < 2.26, ≥ 2.26 mmol/L)

Note that the minimum/maximum category is used, rather than the category of the minimum/maximum value. The two may be different due to variation in the reference range.

No statistical tests will be performed for this analysis.

10.3.2.3 Assessment of Potentially Clinical Significant Laboratory Values

The criteria for potentially clinically significant laboratory values will be determined by CTCAE criteria of Grade 2, Grade 3, Grade 4 and ≥ Grade 3 (if applicable), with a grade worsening compared to baseline. Toxicity grading scale is based on National Cancer Institute Common Toxicity Criteria (NCI CTC) AE version 5.0. For the parameters with no quantitative grading available in version 5.0, CTCAE version 4.03 will be used. The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory values will be summarized by treatment groups.

10.3.2.4 Assessment of Liver Elevations

According to FDA's Guidance for Industry "Drug-Induced Liver Injury: Premarketing clinical evaluation" (July 2009), when aminotransferase abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation > 2 × ULN), in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for the drug to cause severe DILI.

For the purpose of assessing for potential Hy's law cases, the frequencies and percentages of subjects with post baseline liver specific function test values that meet the following criteria of potential clinical interest will be summarized by treatment groups:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 10 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN

- AST ≥ 10 × ULN
- AST ≥ 20 × ULN
- TBL ≥ 2 × ULN
- Alkaline phosphatase ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 1.5 × ULN
- ALT and/or AST ≥ 3 × ULN and concurrent TBL ≥ 2 × ULN

10.3.3 Analysis of Long-Term Laboratory Data

10.3.3.1 Assessment of Clinical Laboratory Variables

Analyses of hematology, chemistry, and urinalysis variables which are measured longitudinally will be performed by visits and by treatment group sequences as described in Section 10.1. For each analysis, the following summary statistics of visit values will be presented for each treatment group sequence: sample size, mean, standard deviation, minimum, median and maximum.

Analyses will be performed for change from baseline in hemoglobin, lymphocytes, neutrophils, creatinine, and creatine phosphokinase (CPK).

10.3.3.2 Assessment of Potentially Clinical Significant Laboratory Values

Long-term laboratory data will be summarized based on the number and percentage of subjects meeting the criteria for potentially clinical significant laboratory values and by the actual treatment received at the time of the event occurrence. The treatment groups are the same as the ones for long-term AE analysis as described in Section 10.2.2. A subject can be counted under different treatment groups if he/she was on placebo from baseline to Week 24 and then started upadacitinib 15 or 30 mg at Week 24 and experienced potentially clinical significant laboratory values under different treatment groups.

In the evaluation of potentially clinically significant laboratory values, the baseline value will be determined by the last non-missing measurement recorded on or before the date of the first dose of study drug in the corresponding treatment group (which may be different than the first dose of study drug received in the study). For example, for a subject who started on placebo and switched to upadacitinib 15 mg QD at Week 24, lab values under upadacitinib 15 mg QD exposure would be evaluated against the baseline value defined as the last non-missing measurement recorded on or before the date of the first dose of upadacitinib 15 mg QD.

A listing of all subjects with any laboratory determination meeting CTCAE criteria of Grade 2 or above with a grade worsening compared to baseline will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

10.3.3.3 Assessment of Liver Elevations

The frequencies and percentages of subjects with post-baseline liver-specific function test values that meet the following criteria of potential clinical interest will be summarized by the actual treatment received at the time of the event occurrence, as described in Section 10.2.2.

A subject can be counted under different treatment groups if he/she was on placebo from baseline to Week 24 and then started upadacitinib 15 or 30 mg at Week 24 and experienced potentially clinical significant laboratory values under different treatment groups.

A listing of potentially clinically significant liver elevations based on criteria specified above will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

10.4 Analysis of Vital Signs

10.4.1 Variables and Criteria Defining Abnormality

Vital sign variables include sitting systolic blood pressure, sitting diastolic blood pressure, pulse rate, and weight. The criteria for potentially clinically significant vital sign findings are presented in Table 11.

Table 11. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 10 mmHg from Baseline
	High	Value ≥ 100 mmHg and increase ≥ 10 mmHg from Baseline
Pulse	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Weight	High	> 7% increase from baseline
	Low	> 7% decrease from baseline

10.4.2 Analysis of Vital Signs Through Week 24

Analyses of vital sign variables which are measured longitudinally will be performed by visits and by the treatment groups of upadacitinib 15 mg QD, upadacitinib 30 mg QD, and the combined placebo group. For each analysis, the following summary statistics will be presented for each treatment group: sample size, mean, standard deviation, minimum, median, and maximum.

The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized by treatment groups.

10.4.3 Analysis of Long-Term Vital Signs

Analyses of vital signs variables which are measured longitudinally will be performed by visits and by treatment group sequences as described in Section 10.1. For each analysis,

the following summary statistics will be presented for each treatment group: sample size, mean, standard deviation, minimum, median, and maximum.

Long-Term vital signs will also be summarized based on the number and percentage of subjects meeting the criteria for potentially clinical significant vital sign values and by the actual treatment received at the time of the event occurrence. The treatment groups are the same as the ones for long-term AE analysis as described in Section 10.2.2. A subject can be counted under different treatment groups if he/she was on placebo from baseline to Week 24 and then started upadacitinib 15 or 30 mg at Week 24 and experienced potentially clinical significant laboratory values under different treatment groups. In the evaluation of potentially clinically significant vital sign values, the baseline value will be determined by the last non-missing measurement recorded on or before the date of the first dose of study drug in the corresponding treatment group, similarly as described in Section 10.3.3.2.

A listing of all subjects with any vital sign values meeting the criteria for potentially clinically significant vital signs will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

11.0 References

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4. Ratitch B, Lipkovich O'Kelly M. Combining analysis results from multiply imputed categorical data. In: Conference Proceedings from PharmaSUG 2013. Paper SP03. Chicago, IL: May 12 - 15; 2013.

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Appendix A. SAS Procedure for Mantel-Haenszel Test

A SAS procedure, the Proc Freq, will be used to compute the statistics using the Mantel-Haenszel method.[2] Risk difference, 95% CI and p value will be provided through the program.

SAS code example:

```
title 'Placebo vs ABT-494 30 mg QD';
proc freq data= wk12_nri;
where TRTP='Placebo'|TRTP='ABT-494 30 mg QD';
table TRTP*aval/ nopercent nocol chisq riskdiff(cl=wald)
alpha=0.05;
run;


title2 'For p-values';
proc freq data=wk12_nri;
where TRTP='Placebo'|TRTP='ABT-494 30 mg QD';
tables DMARDBL*TRTP*aval/ cmh;
run;
```

Appendix B. Tipping Point Analysis for ACR20 at Week 12

To assess the robustness of the primary analysis using NRI data handling, tipping point analysis is conducted on the primary endpoint ACR20. The analysis is conducted on the FAS using As Observed data handling.

The tipping point analysis will be performed by multiple imputations using logistic regression, allowing the imputed ACR response rate to systematically vary from 0% to 100% in both upadacitinib and placebo, respectively. This will be accomplished by modifying the predicted probabilities for the responses through shifting the log odds ratios,[3] then directly sampling the missing ACR20 response from the Bernoulli distribution with the modified probabilities.

For each pair of shift parameters, the same CMH method used for the primary endpoint will be performed on each of the multiple imputed datasets to obtain the results for each comparison of the upadacitinib treatment group versus the placebo group. Because chi-square distribution of CMH test statistic is skewed from the normal distribution, to combine the results from the CMH test using Rubin's method, a transformation will be conducted to normalize the CMH statistic.[4] These transformed results will be then aggregated using Rubin's method to get *P*-values.

Appendix C. Tipping Point Analysis for Key Secondary Continuous Endpoint

To assess the impact of potential departures from the missing-at-random assumption, tipping point analyses are conducted as a sensitivity check for change from baseline in the key secondary continuous endpoint HAQ-DI.

The tipping point analyses are two-dimensional, i.e., assumptions about the missing outcomes on each upadacitinib dose group and the placebo group are allowed to vary independently. In addition, the focus is on scenarios where missing outcomes on upadacitinib are worse than the imputed values on upadacitinib, while missing outcomes on placebo are better than the imputed values on placebo. Missing values are first imputed via MI under MAR (where the MI imputation is performed upon AO data), and then a shift parameter is applied to the imputed values (a different shift parameter may be specified for each treatment group). This is implemented by PROC MI using the MNAR statement.

More specifically, PROC MI using the fully conditional specification (FCS) method will be performed to impute any missing value and therefore does not rely on a monotone missing pattern. In fact, the FCS method can handle any arbitrary missing data pattern. Treatment is included in the FCS imputation model to enable sampling conditional on treatment groups. Additionally, the imputation model includes stratification factor of current use of non-biologic DMARD (yes/no), gender, race (white vs. non-white), age, baseline BMI, geographic regions, duration of PsA diagnosis and the baseline value of the endpoints of interest, as well as longitudinal response observed at any other visits.

For a given pair of shift parameters, the SAS code example is as follows:

```
PROC MI DATA=DATA_WIDE OUT=DATA_WIDE_BOUNDED NIMPUTE=20
SEED=12345;

  CLASS TRTP &COVCAT;
  FCS;
  By trtp;
  VAR &COVCON &COVCAT WEEK_2 WEEK_4 WEEK_8 WEEK_12;
MNAR ADJUST (WEEK_12 / SHIFT=&SJ1
ADJUSTOBS=(TRTP='PLACEBO'));
```

```
    MNAR ADJUST (WEEK_12 / SHIFT=&SJ2 ADJUSTOBS=(TRTP='UPA
    15MG'));

RUN;
```

Note: The input dataset is in wide format. TRTP denotes the treatment group. &COVCON denotes baseline continuous covariates including baseline age, baseline BMI, duration of PsA diagnosis and baseline value of the endpoint of interest. &COVCAT denotes categorical covariates including current use of non-biological DMARD gender, race, and regions. WEEK_2, WEEK_4, WEEK_8, WEEK_12 denote the observed values at each visit. &SJ1 and &SJ2 denote the shift parameters for the placebo group and upadacitinib 15 MG group respectively.

In cases where the shifted values are smaller than the minimum or larger than maximum value of the endpoint, (i.e., out of range), the minimum or maximum value of the endpoint is used in further analysis steps. For each pair of shift parameters, the SAS procedure PROC MIXED is used for ANCOVA model with Huber-White sandwich errors which includes the fixed effects of treatment, the stratification factor of current DMARD use and the continuous fixed covariate of baseline measurement on each of the multiple imputed datasets to obtain the results for each upadacitinib treatment group versus the placebo group comparison. These results will be aggregated using Rubin's method to get p-values.

If one pair of shift parameters are found to just reverse the study conclusion, in terms of p-value larger than 0.05 (the original p-value < 0.05), then the shift parameters are identified as the tipping point. The results for a grid of shift parameter combinations are provided in tabular format.

The SAS code example of the data imputation step for tipping point analysis using MI is provided above. The SAS code example for the analysis and results combination step using PROC MIXED and PROC MIANALYZE is as follows:

```
PROC MIXED DATA=ALL EMPIRICAL;
    ODS OUTPUT LSMEANS=MIXEDLSMEANS DIFFS=DIFF;
    BY Shift1 Shift2 _IMPUTATION_;
    CLASS TRTP STRATA USUBJID;
    MODEL CHG = BASELINE TRTP STRATA / SOLUTION;
    LSMEANS TRTP / CL PDIFF DIFF;
    REPEATED /SUBJECT=USUBJID;
RUN;
```

```
DATA DIFF1;
    SET DIFF;
    COMPARISON= TRTP||' VS '||LEFT(_TRTP);
RUN;

PROC SORT DATA=DIFF1; BY COMPARISON Shift1 Shift2 _IMPUTATION_; RUN;

PROC MIANALYZE DATA=DIFF1;
    ODS OUTPUT PARAMETERESTIMATES=GROUP_OUTPUT;
    BY comparison shift1 shift2;
    MODELEFFECTS ESTIMATE;
    STDERR STDERR;
RUN;

/* Comparison of "UPA 15 mg" vs. "Placebo" */
data miparm1;
set GROUP_OUTPUT;
if comparison='1            VS            2' then output miparm1;
run;

proc transpose data=miparm1(keep= Shift1 Shift2 Probt)
out=wide_miparm1;
by shift1;
id shift2;
var Probt;
run;
```

Note: The input dataset ALL includes all (# of shift1 parameters) * (# of shift2 parameters) * (# of imputations in MI) imputed datasets. TRTP denotes the treatment group and STRATA denotes the stratification factor used in analysis. CHG denotes the change from baseline value and BASELINE denotes the baseline value.

Appendix D. Exposure Adjusted AE Rate Difference and Normal Approximation Based 95% Confidence Interval (Liu, F et al. 2006[5])

Assume the occurrence of TEAE of special interest follows a Poisson distribution and let λ denote the rate of occurrence of TEAE under the total exposure time for a treatment group. Let n_1 and n_2 be the number of AEs reported in an upadacitinib dose group and the combined placebo group, respectively. Let T_1 and T_2 be the total number of days exposed to study drug summed across all treated subjects in an upadacitinib dose group and the combined placebo group. Under the assumption that n1 and n2 follow independent Poisson distribution with parameters $\lambda_1 T_1$ and $\lambda_2 T_2$, the $\hat{\lambda}_1 = n_1/T_1$ and $\hat{\lambda}_2 = n_2/T_2$. So the exposure adjusted TEAE rate difference can be estimated by

$$\theta = \hat{\lambda}_1 - \hat{\lambda}_2$$

Using normal approximation, the 95% confidence interval can be calculated by

$$\hat{\lambda}_1 - \hat{\lambda}_2 \pm Z_{\alpha/2}\hat{\sigma}$$

where $\hat{\sigma} = \sqrt{n_1/T_1^2 + n_2/T_2^2}$

Document Approval

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