1.0 Title Page

Statistical Analysis Plan

Study M14-663

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

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2.0 Table of Contents

1.0 Title Page 1
2.0 Table of Contents 2
3.0 Introduction 7
4.0 Study Objectives, Design and Procedures 7
4.1 Objectives 7
4.2 Overall Study Design and Plan 8
4.3 Sample Size 24
4.4 Interim Analysis 24
4.5 Data Monitoring Committee (DMC) Activities 24
5.0 Analysis Populations and Analysis Windows 25
5.1 Analysis Populations 25
5.2 Analysis Windows 25
5.3 Variables Used for Stratification of Randomization 28
6.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications 28
6.1 Demographic and Baseline Characteristics 28
6.2 Medical History 31
6.3 Prior Treatment and Concomitant Medications 31
6.4 Protocol Deviations 32
7.0 Patient Disposition 32
8.0 Study Drug Exposure and Compliance 34
8.1 Compliance 35
9.0 Efficacy Analysis 36
9.1 General Considerations 36
9.1.1 Efficacy Analysis at Different Phases of the Study 36
9.1.2 Definition of Missing Data Imputation 37
9.2 Efficacy Analysis for Period 1 38
9.2.1 Primary Efficacy Analysis 38
9.2.2 Sensitivity Analysis of Primary Efficacy Variables 39
9.2.3 Key Secondary Efficacy Analyses 39
9.2.4 Exploratory Efficacy Analyses 40

9.2.5 Handling of Multiplicity 41
9.2.6 Efficacy Subgroup Analysis 41
9.2.7 Summary of Efficacy Analysis for Period 1 42
9.3 Long Term Efficacy Analysis 45
9.4 Efficacy Variables Definitions and Conventions 47
9.4.1 ACR Criteria 47
9.4.2 Joint Evaluation 50
9.4.3 Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS) 51
9.4.4 Physician's Global Assessment of Disease Activity Visual Analog Scale (VAS) 52
9.4.5 Patient's Global Assessment of Pain 52
9.4.6 Disease Activity Score (DAS28) 52
9.4.7 Simplified Disease Activity Index (SDAI) 53
9.4.8 Clinical Disease Activity Index (CDAI) 53
9.4.9 Clinical Remission (CR) and Low Disease Activity (LDA) 54
9.4.10 ACR/EULAR Boolean Remission 54
9.4.11 Disability Index of Health Assessment Questionnaire (HAQ-DI) 55
9.4.12 EuroQoL-5D (EQ-5D-5L) 55
9.4.13 Form SF-36v2 56
9.4.14 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) 56
9.4.15 Work Instability Scale for Rheumatoid Arthritis (RA-WIS) 56
10.0 Safety Analysis 57
10.1 General Considerations 57
10.2 Analysis of Adverse Events 58
10.2.1 Treatment-Emergent Adverse Events 58
10.2.2 Analysis of Adverse Events for Period 1 59
10.2.2.1 Adverse Events Overview 59
10.2.2.2 Adverse Events by System Organ Class and Preferred Term 60
10.2.2.3 TEAEs by Maximum Severity 60
10.2.2.4 TEAEs by Relationship 61

10.2.2.5 Frequent (≥ 5%) Adverse Events and Reasonably Possibly Related Adverse Events by System Organ Class and Preferred Term 61
10.2.2.6 Adverse Events of Special Interests 61
10.2.3 Analysis of Long Term Adverse Event Rates 63
10.2.3.1 Overview of Adverse Events Rates per 100 Patient-Years of Study Drug Exposure 63
10.2.3.2 Adverse Events Rates per 100 Patient-Years of Study Drug Exposure by SOC and PT 64
10.2.3.3 Adverse Events of Special Interest Rates per 100 Patient-Years of Study Drug Exposure 65
10.2.3.4 Listing of Serious Adverse Events (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation 66
10.3 Analysis of Laboratory Data 66
10.3.1 Variables and Units 66
10.3.2 Analysis of Laboratory Data for Period 1 68
10.3.2.1 Assessment of Mean Change from Baseline and Mean Percentage Change from Baseline in Clinical Laboratory Variables 68
10.3.2.2 Assessment of Shift from Baseline in Clinical Laboratory Variables 69
10.3.2.3 Assessment of Potentially Clinical Significant Laboratory Variables 69
10.3.2.4 Assessment of Liver Elevations 70
10.3.3 Analysis of Long Term Laboratory Data 71
10.3.3.1 Assessment of Mean Change from Baseline and Mean Percentage Change from Baseline in Clinical Laboratory Variables 71
10.3.3.2 Assessment of Potentially Clinical Significant Laboratory Values 71
10.3.3.3 Assessment of Liver Elevations 72
10.4 Analysis of Vital Signs 73
10.4.1 Variables and Criteria Defining Abnormality 73
10.4.2 Analysis of Vital Sign for Period 1 73
10.4.3 Analysis of Long Term Vital Sign 74
10.5 Analysis of ECG Parameters 74
10.5.1 Variables 74

11.0 Appendix 75
12.0 References 87

List of Tables

Table 1. Study Activities (Period 1) 14
Table 2. Study Activities – Optional Samples for Exploratory Research and Validation Studies (Period 1 Only) 19
Table 3. Studies Activities (Period 2) 20
Table 4. Analysis Windows for Efficacy Analysis for Period 1 (for ACR Components and Morning Stiffness) 26
Table 5. Analysis Windows for Safety Analysis for Period 1 (for Labs and Vital Signs) 27
Table 6. Analysis Windows for Efficacy Analysis for Period 1 (for EQ-5D-5L, SF-36, FACIT-F and RA-WIS) 27
Table 7. Analysis Windows for In Vivo Pharmacodynamic Biomarkers 27
Table 8. Subgroups for Efficacy Analysis 42
Table 9. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis in Period 1 43
Table 10. Summary of Efficacy Variables and Corresponding Analyses for Long Term Efficacy Analysis 47
Table 11. Anatomical Joints Assessed for Calculation of Tender and Swollen Joint Counts (TJC68 and SJC66) 51
Table 12. Anatomical Joints for DAS28 (CRP) Calculation 53
Table 13. AESI for Upadacitinib with SMQs/CMQs/PTs Searches 62
Table 14. List of Laboratory Variables 66
Table 15. Criteria for Potentially Clinically Significant Vital Sign Findings 73

List of Figures

Figure 1. Period 1 Study Design 10
Figure 2. Period 2 Study Design 11

List of Appendices

Appendix A. OMERACT Criteria 76

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the Data and Statistical Science Department for Upadacitinib (ABT-494) Study M14-663. It provides details to further elaborate statistical methods as outlined in the protocol. Pharmacokinetic and biomarker analyses will be performed separately and reported in a separate document.

Unless noted otherwise, all analyses will be performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

Period 1

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

Period 2

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

4.2 Overall Study Design and Plan

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

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

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

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

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

- Group 6: Placebo, N = 16 (Period 1) → ABT-494 30 mg QD (Period 2)

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

Subjects must have been on a stable dose of csDMARD(s) for ≥ 4 weeks prior to the first dose of study drug and must remain on a stable dose until Week 24; the csDMARD dose may be decreased only for safety reasons. Subjects who do not achieve CDAI ≤ 10 at Week 24 should have background medication(s) adjusted or initiated after assessments for Week 24 have been completed. Starting at Week 24 (after Week 24 assessments have been performed), initiation of or change in corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or adding or increasing doses in up to 2 csDMARDs (concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide) is allowed as per local label.

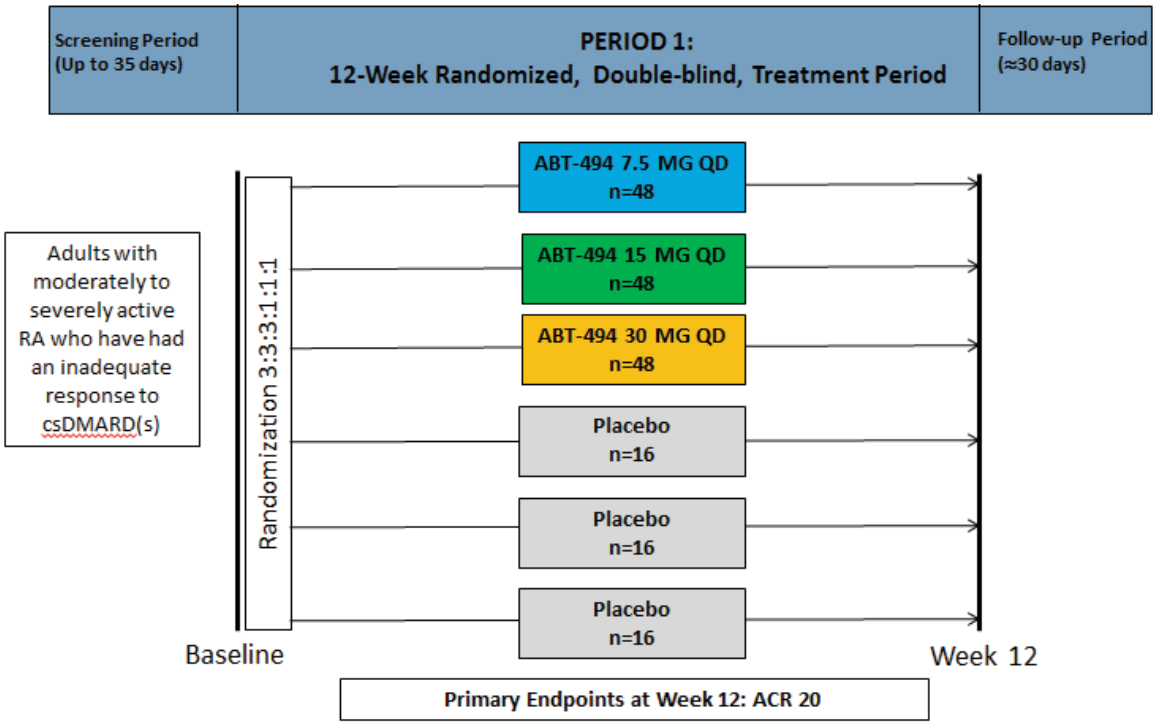
Subjects with prior exposure to at most one bDMARD for RA may be enrolled in the study (up to 20% of total study population) after the required washout period is satisfied and if they have limited exposure (< 3 months), OR response to bDMARD but had to discontinue that bDMARD due to intolerability (regardless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

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

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12). Additional unblinded analyses may be conducted for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study (Periods 1 and 2).

Study design schematics of Period 1 and Period 2 are shown in Figure 1 and Figure 2 respectively.

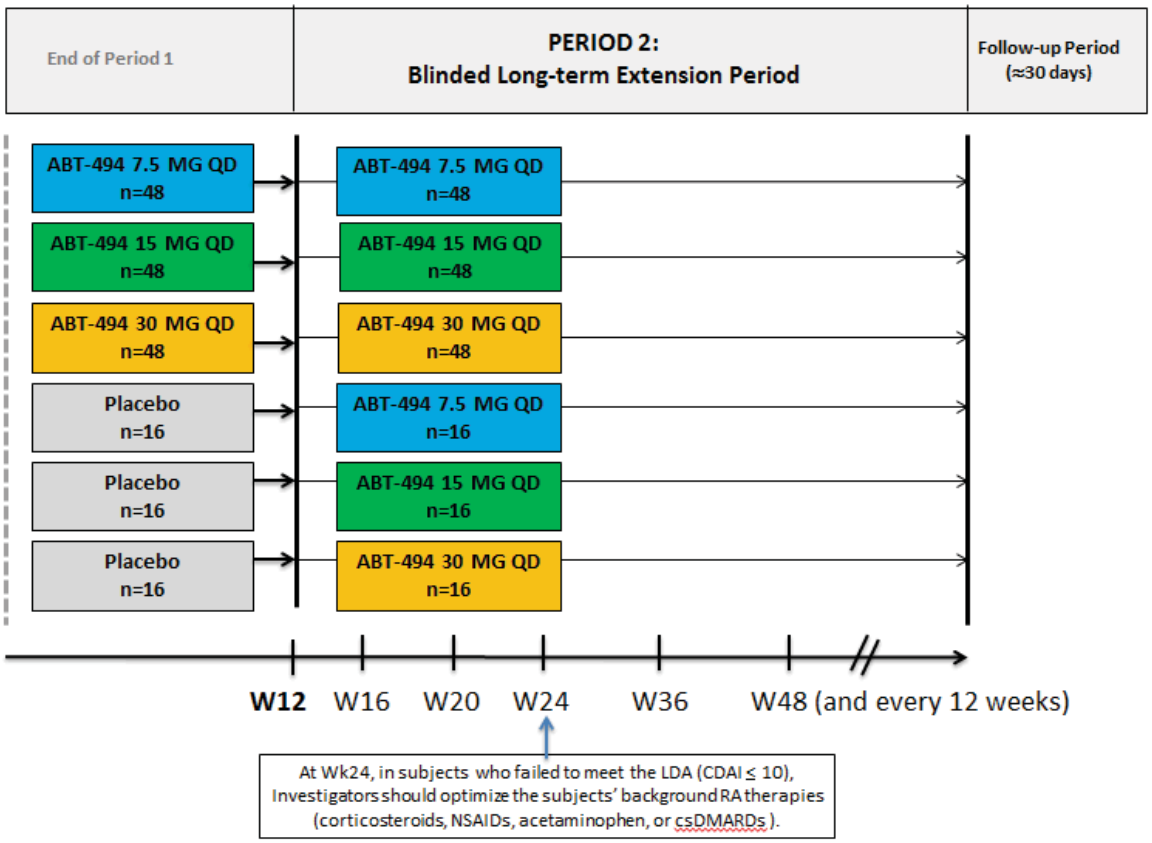
Figure 1. Period 1 Study Design



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

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

Figure 2. Period 2 Study Design



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

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

The study activities of Period 1 and Period 2 are presented in Table 1, Table 2 and Table 3.

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 the protocol. Lab values can be re-tested once during the

screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Subjects that screen fail for re-tested laboratory values may be re-screened only after consultation with the AbbVie TAMD. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

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

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

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

Period 2 (Blinded Long-Term Extension Period [Until Regulatory Approval of RA Indication in Japan])

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

Starting at Week 24 and thereafter, study drug will be discontinued for subjects who fail to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits.

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

Subjects may withdraw from the study completely at any time. If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, if the subject is willing, a 30-day follow-up phone call may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Follow-Up Visit

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

Subjects will complete the 30 day-Follow-Up Visit when they have either: 1) Completed the last visit of Period 1 (Week 12), but decided not to participate in Period 2; OR, 2) Completed the last visit of Period 2; OR, 3) Prematurely discontinued study drug and study participation. If a Premature Discontinuation visit has already occurred, then the 30 day Follow-Up visit may be a telephone call if a site visit is not possible.

Table 1. Study Activities (Period 1)

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

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

Activity	Screening D –35 to D –1	BL D1[b]	Wk 1 D8	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 or PD[a] D85	30-Day F/U Visit[c]
Physician's Global Assessment (PhGA)		X	X	X	X	X	X	
TJC68/SJC66	X	X	X	X	X	X	X	
Serum pregnancy test at central lab[m]	X							
Local urine pregnancy test[n]		X		X	X	X	X	X
Central lab tests hsCRP[o], Blood chemistry[p], Hematology (CBC), Urinalysis[q]	X	X	X (hsCRP only)	X	X	X	X	X
ESR (local lab)	X	X	X	X	X	X	X	
Other central lab tests Rheumatoid factor, Anti-CCP autoantibodies, HBV/HCV screening[r], beta-D-glucan, GFR by simplified 4-variable MDRD formula	X							
HIV[s]	X							
VZV skin test[t] and VZV specific IgG[t]	X							
IgG and IgM (central lab)		X				X		
Blood samples for ABT-494 PK assay			X[u,v]	X[u]	X[w]	X[w]	X[w]	
In vivo pharmacodynamic biomarkers		X				X	X[x]	X
Blood samples for exploratory research and validation studies (optional – see Table 2)[y]	X		X	X		X		
Randomization/Treatment group assignment		X						

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

Activity	Screening D –35 to D –1	BL D1[b]	Wk 1 D8	Wk 2 D15	Wk 4 D29	Wk 8 D57	Wk 12 or PD[a] D85	30-Day F/U Visit[c]
Dispense study drug and subject dosing diary		X			X	X	X[z]	
Review and retain a copy of subject dosing diary and perform drug reconciliation					X	X	X	

BL = Baseline Visit; CBC = complete blood count; CCP = cyclic citrullinated peptide; D = Day; ECG = electrocardiogram; EQ-5D-5L = EuroQoL-5D; ESR = erythrocyte sedimentation rate; F/U = Follow-up; GFR = Estimated glomerular filtration rate; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; MDRD = Modification of Diet in Renal Disease; PD = Premature Discontinuation; PhGA = Physician's Global Disease Activity; PK = pharmacokinetics; PPD = purified protein derivative; PtGA = Patient's Global Assessment of Disease Activity; SAE = serious adverse event; SJC = Swollen Joint Count; SF-36 = 36-Item Short Form Health Survey; TB = tuberculosis; TJC = Tender Joint Count; VAS = visual analog scale; VZV = varicella-zoster virus; Wk = Week

a. If a subject prematurely discontinues study drug treatment and study participation, the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation.

b. The Baseline visit procedures will serve as the reference for all subsequent visits with the exception of the ECG which will be obtained at Screening only and used as the baseline reference.

c. This visit is 30 days after last dose of study drug for those subjects who complete Period 1 and do NOT enter Period 2. A 30-day follow-up phone call may be allowed for subjects who have completed PD visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

d. Obtain prior to performing any study related procedures.

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

f. Collect serious adverse events and protocol-related non-SAE that occur after a subject signs the informed consent, prior to the first dose of study drug.

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

h. Study Procedures TB Testing for specific requirements for TB testing and TB Prophylaxis. The Latent TB risk factor assessment and TB Testing will be performed in case of Premature Discontinuation visit but not at Week 12.

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

i. The chest x-ray will not be required if a subject had a previous normal chest-x-ray within 90 days of Screening, provided that all source documentation is available at the site (Chest X-Ray for specific requirements). Obtain chest x-ray at PD for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline.

j. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all source documentation is available. For subjects who do not enter Period 2 or prematurely discontinue from the study, an ECG will be performed. 12-Lead ECG for additional details.

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

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

m. For all women of childbearing potential, collect serum for pregnancy test only at screening. If serum pregnancy test comes back borderline, a repeat test is necessary (pregnancy is an exclusion criterion). Study Procedures Pregnancy Test for additional details.

n. For all women of child bearing potential, collect urine for pregnancy test at Baseline and all subsequent visits except Week 1. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study. Study Procedures Pregnancy Test for additional details.

o. hsCRP results will remain blinded to Sponsor, Investigator, study site personnel, and the subject for all visits except Screening. Investigator should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigator should also refrain from locally testing procalcitonin except for safety evaluations of signs and symptoms of infection management of and adverse events.

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

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

r. In HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV-DNA PCR test should be performed every 12 weeks (Week 12 and every 12 weeks thereafter). The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-DNA is observed. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+).

s. Subjects will be tested for antibodies to HIV at Screening, and it should be documented that the test has been performed. This testing is to be done centrally or at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

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

t. VZV skin test will be performed locally at Screening. VZV specific IgG should be measured centrally at Screening. If a subject had a VZV skin test within 90 days prior to Screening and source documentation is available, the test does not need to be repeated. Alternative methods other than VZV skin test are also acceptable to assess the cell-mediated immune status to VZV (e.g., IGRA). In case of shortage or inability to supply the tests to assess the cell-mediated immune status to VZV, only IgG-class antibodies specific to VZV will be tested at Screening.

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

v. Subjects who participate in the intensive pharmacokinetic assessment will be asked to fast for a minimum of 8 hours prior to the study visit selected for the intensive PK assessment (Week 1, 2, 4, 8 or 12) and not to take the drug dose on the day of intensive PK assessment before coming for the visit. Subjects will be dosed during the visit and will continue fasting for 4 hours after dosing. No food or drinks will be allowed during fasting except water to quench thirst. Blood samples will be collected during the study visit selected for the intensive PK assessment prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose.

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

x. In vivo pharmacodynamic biomarkers sample will be collected in case of Premature Discontinuation visit but not at Week 12.

y. Samples only collected if subject provides written consent.

z. For subjects entering Period 2.

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

Table 2. Study Activities – Optional Samples for Exploratory Research and Validation Studies (Period 1 Only)

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

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

a. The sample is preferred to be collected at BL, but can be drawn at any time during the subject's participation.

b. Based on the value of the different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches.

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

Table 3. Studies Activities (Period 2)

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

Table 3. Studies Activities (Period 2) (Continued)

Activity	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Monthly	Every 12 Weeks Until Study Completion[a]	Every 24 Weeks Until Study Completion[a]	Every 48 Weeks Until Study Completion[a]	Final/ PD Visit	30-Day F/U Visit/ Call[b]
In-home urine pregnancy test[m]						X					
Central lab tests hsCRP[n] Blood chemistry[o] Hematology (CBC) Urinalysis[p]	X	X	X	X	X		X			X	X
ESR (local lab)	X	X	X	X	X		X			X	
HBV screening[q]			X	X	X		X				
In vivo pharmacodynamic biomarkers			X		X						
Dispense study drug and subject dosing diary	X	X	X	X	X		X				
Review and retain a copy subject dosing diary and perform drug reconciliation	X	X	X	X	X		X			X	

BL = Baseline Visit; CBC = complete blood count; csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; ECG = electrocardiogram; F/U = Follow-up; HAQ-DI = Health Assessment Questionnaire – Disability Index; hsCRP = high-sensitivity C-reactive protein; NRS = numerical rating scale; PD = Premature Discontinuation; PhGA = Physician's Global Disease Activity; PPD = purified protein derivative; PtGA = Patient's Global Assessment of Disease Activity; RCT = randomized controlled trial; SAE = serious adverse event; SJC = Swollen Joint Count; TB = tuberculosis; TJC = Tender Joint Count; VAS = visual analog scale; Wk = Week

a. Every 12, 24, or 48 weeks from the Week 48 visit.

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

Table 3. Studies Activities (Period 2) (Continued)

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

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

e. TB testing should be performed every 48 weeks after Week 48 and at PD in subjects with previous negative Quantiferon and/or PPD tests. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines. TB Testing/TB prophylaxis for additional details.

f. Obtain chest x-ray every 48 weeks after Week 48 and PD for subjects with TB risk factors as identified by the TB risk assessment form, or for subjects living in areas endemic for TB, or for subjects with a newly positive QuantiFERON-TB Gold test (and/or PPD skin test) after baseline.

g. ECGs will be performed every 48 weeks after Week 48 and for subjects who prematurely discontinue from the study. An ECG may be performed at any visit if deemed necessary by the Investigator.

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

i. A full physical exam is required every 24 weeks after Week 48. A symptom-directed physical exam may be performed when necessary.

j. Starting at Week 24 and thereafter, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits should be discontinued from the study.

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

l. For women of childbearing potential, a urine pregnancy test will be performed at all visits and monthly at home between scheduled study visits. Pregnant subjects must discontinue from the study. Study Procedures Pregnancy Test for additional details.

m. Starting at Week 24, for women of childbearing potential, in-home urine pregnancy tests will be performed monthly. The results of the monthly at home tests will be communicated to the site. If a urine pregnancy test is positive, the subject must stop dosing, come in to the clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory.

n. hsCRP results from the central laboratory will remain blinded to Sponsor, Investigator, study site personnel, and the subject. Treatment assignment may be unblinded to Sponsor only when the last subject completes Period 1 (Week 12 visit) for an analysis for regulatory purposes. For safety evaluations of signs and symptoms of infection and management of adverse events, the Investigator may locally test procalcitonin. However, results of tests such as hsCRP, serum amyloid A and procalcitonin may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. It should also be noted that any hsCRP, CRP, serial SAA, or serial procalcitonin local tests reported to the Investigator will be recorded as protocol deviations.

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

Table 3. Studies Activities (Period 2) (Continued)

p. Dipstick urinalysis will be completed by the central lab at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

q. In HBs Ab positive (+) subjects and/or HBc Ab positive (+) subjects, HBV-DNA PCR test should be performed in every 12 weeks. The investigator has to consult with the medical expert of the sponsor in case where the recurrence of HBV-DNA is observed. This measure is not necessary in case of the patients with the history of HBV vaccine and HBs Ab positive (+).

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

4.3 Sample Size

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

4.4 Interim Analysis

An unblinded analysis will be conducted after all subjects have completed Period 1 (Week 12). Additional unblinded analyses may be conducted for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of the study (Periods 1 and 2).

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 meet any major protocol deviations during 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 major protocol deviations.

Major protocol deviations (ICH deviation and other clinically significant non-ICH deviation) will be identified prior to 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 are assigned to a treatment group based on the "as treated" treatment group, regardless of the treatment randomized. The "as treated" is determined by the treatment the subject received during the majority of the subject's drug exposure time in the study.

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 4 and Table 6 (depending on the different visit schedules of different endpoints). Visit windows for protocol-specified visits in Period 2 are defined similarly.

Table 4. Analysis Windows for Efficacy Analysis for Period 1 (for ACR Components and Morning Stiffness)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
1	2	8	11
2	12	15	22
4	23	29	43
8	44	57	71
12	72	85	min (99, first dose date of Period 2)

a. Day of first dose of study drug.

Table 5. Analysis Windows for Safety Analysis for Period 1 (for Labs and Vital Signs)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
2	2	15	22
4	23	29	43
8	44	57	71
12	72	85	min (99, first dose date of Period 2)

a. Day of first dose of study drug.

Table 6. Analysis Windows for Efficacy Analysis for Period 1 (for EQ-5D-5L, SF-36, FACIT-F and RA-WIS)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
4	2	29	57
12	58	85	min (127, first dose date of Period 2)

a. Day of first dose of study drug.

Table 7. Analysis Windows for In Vivo Pharmacodynamic Biomarkers

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
8	2	57	71
12	72	85	min (99, first dose date of Period 2)

a. Day of first dose of study drug.

5.3 Variables Used for Stratification of Randomization

The randomization of the study will be stratified based on prior exposure to bDMARD (yes/no).

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

6.1 Demographic 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 (Asian, Other)
- Weight (kg)
- Weight Categories (< 60 kg, ≥ 60 kg and < 45 kg, [45, 60], > 60 kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Body Mass Index (BMI) Category (kg/m^2) (BMI < 25 vs BMI ≥ 25)

RA Medical History and Characteristics

- Duration of RA Symptoms in years
- Duration of RA Diagnosis in years
- Duration of RA Diagnosis Categories (< 5 year or ≥ 5 year)
- Prior exposure to bDMARDs (Yes or No)

- Corticosteroids use at baseline (yes, no)
- Oral steroid dosing (prednisone equivalent) at baseline
- Concomitant csDMARD at baseline (MTX alone, MTX and other csDMARD, csDMARD other than MTX)

ACR and/or DAS Components at Baseline

- 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
- Tender joint count (TJC28) defined as the number of tender joints out of 28 assessed joints used for DAS28 calculation
- Swollen joint count (SJC28) defined as the number of swollen joints out of 28 assessed joints used for DAS28 calculation
- Physician's global assessment of disease activity (mm on a 100-mm horizontal visual analogue scale [VAS])
- Patient's assessment of pain within last week (mm on a 100-mm horizontal (VAS)
- Patient's global assessment of disease activity within last 24 hours (mm on a 100-mm horizontal VAS)
- Health Assessment Questionnaire Disability Index of the (HAQ – DI) (range: 0 to 3)
- High sensitivity C-reactive protein (hsCRP) (mg/L)
- Erythrocyte sedimentation rate (ESR) (mm/hr)

Other Baseline RA Disease Characteristics

- Anti-cyclic citrulliated peptide (Anti-CCP) (units)
- Anti-CCP status: Positive or Negative
- Rheumatoid Factor (RF) (units)
- Rheumatoid Factor (RF) status: Positive or Negative

- DAS28 [hsCRP]
- DAS28 [ESR]
- DAS28 Categories:
  - DAS28 > 5.1 (High Disease Activity)
  - DAS28 ≤ 5.1
- Clinical Disease Activity Index (CDAI)
- CDAI categories:
  - CDAI > 22 (High Disease Activity)
  - CDAI ≤ 22
- Simplified Disease Activity Index (SDAI)
- SDAI categories:
  - SDAI > 26 (High Disease Activity)
  - SDAI ≤ 26

Patient Report Outcomes at Baseline

- Morning stiffness (severity and duration)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Work Instability Scale for Rheumatoid Arthritis (RA-WIS)
- 36-Item Short Form Health Survey (SF-36) Version 2: physical component summary, mental component summary and the 8 sub-domain scores
- EQ-5D-5L

Clinical Tests at Screening

- Chest x-ray
- ECG
- Tuberculin PPD skin test, QuantiFERON TB Gold test
- Hepatitis Testing
- Serum pregnancy test

Immunization History

- BCG immunization
- Herpes Zoster immunization (regardless of Type of vaccine)
- Hepatitis B immunization

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 are categorized as follows based on ICH deviation criteria:

- Those who entered the study even though they did not satisfy the entry criteria
- Those who developed withdrawal criteria during the study and were not withdrawn
- Those who received the wrong treatment or incorrect dose, and
- 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 primary efficacy analysis, Safety Analysis Set for Period 1),
- number of subjects who completed Period 1,
- number of subjects who entered Period 2,
- number of subjects on-going in Period 2 (if applicable),
- number of subjects who completed overall study (Period 1 and Period 2) (if applicable).

This summary will be repeated by site.

Prematurely discontinued study drug details will be further summarized separately for Period 1 and Period 2 as follows.

Period 1

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

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

Subjects may have more than one reason for discontinuing, but only the primary reason will be summarized.

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

Period 2

Period 2 patient dispositions and reason for discontinuation of study drug will be summarized for overall and by actual treatment in Period 2 defined as follows:

1. Upadacitinib (ABT-494) 7.5 mg QD
2. Upadacitinib (ABT-494) 15 mg QD
3. Upadacitinib (ABT-494) 30 mg QD

Among the subjects who entered Period 2, the number and percentage of subjects completed, on-going (if applicable), and prematurely discontinued in Period 2 will be summarized.

For subjects who prematurely discontinued study drug the primary reasons for discontinuation will be summarized by the following categories (as collected in CRF):

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

Subjects may have more than one reason for discontinuing, but only the primary reason will be summarized.

8.0 Study Drug Exposure and Compliance

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

1. Upadacitinib (ABT-494) 7.5 mg QD

   This includes Upadacitinib 7.5 mg QD exposure from subjects starting on Upadacitinib 7.5 mg QD and subjects switching from placebo to Upadacitinib 7.5 mg QD.

2. Upadacitinib (ABT-494) 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 (ABT-494) 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.

4. Placebo

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.

- ≥ 1 weeks
- ≥ 2 weeks
- ≥ 1 month
- ≥ 3 months
- ≥ 6 months
- ≥ 9 months
- ≥ 12 months
- ≥ 18 months
- ≥ 2 years
- ≥ 2.5 years
- ≥ 3 years
- ≥ 4 years

8.1 Compliance

Study drug compliance will be summarized for each treatment group for Period 1. The compliance is defined as the number of tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) during the subject's participation in Period 1 divided by the number of days that the subject was in the Treatment Phase of Period 1.

9.0 Efficacy Analysis

9.1 General Considerations

There are two sets of planned efficacy analysis: efficacy analysis for Period 1 and long-term efficacy analysis. All efficacy analyses will be carried out using the FAS population.

9.1.1 Efficacy Analysis at Different Phases of the Study

Efficacy Analysis for Period 1

Standard efficacy analysis by randomized treatment groups (Upadacitinib 7.5 mg QD, Upadacitinib 15 mg QD, Upadacitinib 30 mg QD and the combined placebo groups) will be performed on efficacy data for Period 1 (up to Week 12). 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. Upadacitinib (ABT-494) 7.5 mg QD
2. Upadacitinib (ABT-494) 15 mg QD
3. Upadacitinib (ABT-494) 30 mg QD
4. Placebo →Upadacitinib (ABT-494) 7.5 mg QD
5. Placebo →Upadacitinib (ABT-494) 15 mg QD
6. Placebo →Upadacitinib (ABT-494) 30 mg QD.

There will be no statistical testing; only descriptive statistics and confidence intervals will be provided.

9.1.2 Definition of Missing Data Imputation

Non-Responder Imputation (NRI) Approach

The NRI approach will categorize any subject who has 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.

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. In addition, the OC will not use values after premature discontinuation of study drug. This sensitivity analysis will only be applied to the analysis in Period 1.

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. Regardless of treatment switching or premature discontinuation of study drug, all observed data will be used in the analysis. The AO analysis will be applied to long term efficacy analysis.

Mixed Effect Model Repeat Measurement (MMRM)

The repeated measure analysis will be conducted using mixed model including observed measurements at all visits. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors at randomization, and the continuous fixed covariates of baseline measurement. An unstructured variance covariance matrix will be used. The parameter estimations is based on assumption of data being missing at random and using the method of restrictive maximum likelihood (REML).

Multiple Imputation (MI)

The MI analysis will impute missing data multiple times under appropriate random variation and thus generate multiple imputed "pseudo-complete" datasets. Results will be aggregated across the multiple imputed datasets, overcoming drawbacks of the single imputation methods. [redacted]

9.2 Efficacy Analysis for Period 1

9.2.1 Primary Efficacy Analysis

The primary endpoint (at Week 12) is ACR20 response at Week 12. Analysis of the primary endpoint will be conducted on the FAS based on randomized treatment groups (Upadacitinib 7.5 mg QD, Upadacitinib 15 mg QD, Upadacitinib 30 mg QD and the combined placebo groups). Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. The dose-response curve will be shown graphically with CI for each dose. Cochran-Armitage test will be conducted for demonstrating non-flat dose response relationship.

Comparisons of the primary endpoint will be made between each Upadacitinib dose and the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bMDARD use. Point estimate, 95% CI using normal approximation and p-value for the treatment comparison will be presented. For the primary analysis, non-responder imputation (NRI) will be used.

9.2.2 Sensitivity Analysis of Primary Efficacy Variables

The primary analysis for point estimate and CI will be repeated using OC 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

Key secondary endpoints at Week 12 are:

1. Change from baseline in DAS28 (CRP);
2. Change from baseline in HAQ-DI;
3. ACR50 response rate;
4. ACR70 response rate;
5. Change from baseline in Short Form-36 (SF-36) Physical Component Score (PCS);
6. Proportion of subjects achieving LDA based on DAS28 (CRP);
7. Proportion of subjects achieving Clinical remission (CR) based on DAS28 (CRP);
8. ACR20 response rate of Week 1;
9. Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F);
10. Change from baseline in Work Instability Scale for Rheumatoid Arthritis (RA-WIS);
11. Change from baseline in morning stiffness (severity).

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

For the major RA continuous endpoints DAS28 and HAQ-DI change from baseline, statistical inference will be conducted using analysis of covariance (ANCOVA) coupled

with MI for missing data handling. Specifically, the ANCOVA model will include treatment as the fixed factor, and the corresponding baseline value and the stratification factor prior bDMARD use (Yes/No) as the covariates. For other continuous endpoints, statistical inference will be conducted using the MMRM model as described in Section 9.1.2, with the main stratification factor being prior bDMARD use (Yes/No). From both the MI and MMRM analyses, the LS mean and 95% CI will be reported for each randomized treatment group; the LS mean treatment difference and associated 95% CI and p-value will be reported comparing each Upadacitinib dose group with the combined placebo group.

9.2.4 Exploratory Efficacy Analyses

Additional efficacy analysis includes the following endpoints at all visits in Period 1:

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

For binary endpoints, point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Point estimate, 95% CI and p-value will be provided for the treatment comparison between each Upadacitinib dose group and the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. The 95% CI will be based on

normal approximation. NRI will be used as primary analysis and OC will be used as sensitivity analysis.

For continuous endpoints, the LS mean and 95% CI will be reported for each randomized treatment group. The LS mean treatment difference and associated 95% CI and p-values between each Upadacitinib dose group and the combined placebo group will be provided using MMRM model with fixed effects of treatment, visit and treatment-by-visit interaction, prior bDMARD use and baseline value as covariate.

9.2.5 Handling of Multiplicity

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

9.2.6 Efficacy Subgroup Analysis

The primary efficacy endpoint will be examined in the subgroups listed in Table 8 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 has fewer than 10% of the planned study size (i.e., < 20 subjects), the subgroup analyses for that variable will not be presented.

Table 8. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	< 40, (40, 65), ≥ 65
Sex	Male or Female
Weight	< 60 kg or ≥ 60 kg and < 45 kg, (45, 60), > 60 kg
BMI	< 25 or ≥ 25
Duration of RA diagnosis	< 5 year or ≥ 5 year
Baseline Rheumatoid Factor Status	Positive or Negative
Baseline Anti-CCP Antibody Status	Positive or Negative
Baseline both RF positive and Anti-CCP positive	Yes or No
Baseline DAS28 [hsCRP)	≤ 5.1 or > 5.1
Prior bDMARD use	Yes or No

9.2.7 Summary of Efficacy Analysis for Period 1

Table 9 below provides the overview of the efficacy analyses for Period 1 to be performed on different endpoints.

Table 9. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis in Period 1

Efficacy Variables	Analysis Method
Primary Variables	
• ACR20 response at Week 12	• The dose-response curve will be shown graphically with CI for each dose and Cochran-Armitage test will be conducted. • Point estimate and 95% CI of the response rate for each Upadacitinib dose group and the combined placebo group. The 95% CI will be based on normal approximation. • Point estimate, 95% CI and p-value for the treatment comparison between each Upadacitinib dose group and the combined placebo group, where the p-value is constructed using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. The 95% CI will be based on normal approximation. • Subgroup analysis. • Imputation: NRI for primary analysis and OC for sensitivity analysis • Analysis Set: FAS and Per Protocol Analysis Set as supportive analysis (NRI only).
Key Secondary Variables	
Binary Endpoints: • ACR50/70 response at Week 12 • ACR20 response at Week 1 • Proportion of subjects achieving LDA based on DAS28 (CRP) at Week 12 • Proportion of subjects achieving Clinical remission (CR) based on DAS28 (CRP) at Week 12	• Point estimate and 95% CI of the response rate for each treatment group. The 95% CI will be based on normal approximation. • Point estimate, 95% CI and p-value for the treatment comparison between each Upadacitinib dose group and the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. The 95% CI will be based on normal approximation. • Imputation: NRI for primary analysis and OC for sensitivity analysis • Analysis Set: FAS

Table 9. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis in Period 1 (Continued)

Efficacy Variables	Analysis Method
Key Secondary Variables (continued)	
Continuous Endpoints: • Change from baseline in DAS28 (CRP) at Week 12 • Change from baseline in HAQ-DI at Week 12	• LS mean, and 95% CI within each treatment group and LS mean, 95% CI and p-values between each Upadacitinib dose group and the combined placebo group using ANCOVA model with treatment, prior bDMARD use and baseline value as covariates. • Imputation: MI • Analysis Set: FAS
• Change from baseline in SF-36 Physical Component Score (PCS) at Week 12 • Change from baseline in FACIT-F • Change from baseline in RA-WIS • Change from baseline in morning stiffness (severity).	• LS mean and 95% CI within each treatment group and LS mean, 95% CI and p-values between each Upadacitinib dose group and the combined placebo group using MMRM model with fixed effects of treatment, visit and treatment-by-visit interaction, prior bDMARD use and baseline value as covariate. • Analysis Set: FAS
Additional Variables (Summarized at all Visits up to Week 12)	
Binary Endpoints: • ACR20/50/70 response rate • Proportion of subjects achieving LDA and CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria	• Point estimate and 95% CI of the response rate for each treatment group. The 95% CI will be based on normal approximation. • Point estimate, 95% CI and p-value for the treatment comparison between each Upadacitinib dose group and the combined placebo group using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use. Nominal p-value will be provided, and the 95% CI will be based on normal approximation. • Imputation: NRI for primary analysis and OC for sensitivity analysis • Analysis Set: FAS

Table 9. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis in Period 1 (Continued)

Efficacy Variables	Analysis Method
Additional Variables (Summarized at all Visits up to Week 12) (continued)	
Continuous Endpoints: • Change from baseline in individual components of ACR response • Change from baseline in DAS28 (CRP) and DAS28 (ESR) • Change from baseline in morning stiffness (severity and duration) • Change from baseline in EQ-5D-5L • Change from baseline in SF-36 • Change from baseline in FACIT-F • Change from baseline in RA-WIS	• LS mean and 95% CI within each treatment group and LS mean, 95% CI and p-values between each Upadacitinib dose group and the combined placebo group using MMRM model with fixed effects of treatment, visit and treatment-by-visit interaction, prior bDMARD use and baseline value as covariate. Analysis Set: FAS

9.3 Long Term Efficacy Analysis

Assessments to evaluate long term efficacy will be analyzed for the following measures at Week 1, 2, 4, 8, 12, 16, 20, 24, 36, 48, and every 12 weeks thereafter until completion of the study.

- ACR20/50/70 response rates;
- Change from baseline in individual components of ACR response;
- Change from baseline in DAS28 (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in morning stiffness (severity and duration);
- Proportion of subjects achieving LDA and proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria;
- Proportion of subjects with no concomitant corticosteroid use (among subjects with corticosteroid use at baseline).

Assessments to evaluate long term efficacy will be analyzed for the following measures at Week 4, 12, 24, 48:

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

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 up to Week 36 and 48.

No missing data imputation will be applied. All efficacy analyses will be based on As Observed (AO) analysis.

Table 10 below provides the overview of the long term efficacy analyses to be performed on different endpoints.

Table 10. Summary of Efficacy Variables and Corresponding Analyses for Long Term Efficacy Analysis

Efficacy Variables	Analysis Method
Binary Endpoints:	
• ACR20/50/70 response by visit • LDA and CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria by visit • Proportion of subjects with no concomitant corticosteroid use (among subjects with corticosteroid use at baseline)	• Point estimate and 95% CI of the response rate for each randomized treatment group sequence • Plot for each randomized treatment group sequence over time • Imputation: AO • Analysis Set: FAS
Continuous Endpoints:	
• Change from baseline in individual ACR components by visit • Change from baseline in DAS28 (CRP) by visit • Change from baseline in DAS28 (ESR) by visit • Change from baseline in morning stiffness (severity and duration) by visit • Change from baseline in EQ-5D-5L by visit • Change from baseline in FACIT-F; • Change from baseline in RA-WIS. • Change from baseline in SF-36 by visit	• Point estimate, 95% CI of mean change from baseline together with SD, Min, Q1, Median, Q3 and Max for each randomized treatment group sequence • Plot for each randomized treatment group sequence over time • Imputation: AO • Analysis Set: FAS

9.4 Efficacy Variables Definitions and Conventions

9.4.1 ACR Criteria

ACR criteria are a commonly used standard criteria set mentioned in the guidance of American College of Rheumatology to evaluate the effectiveness of investigation drug in RA clinical trials. 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).

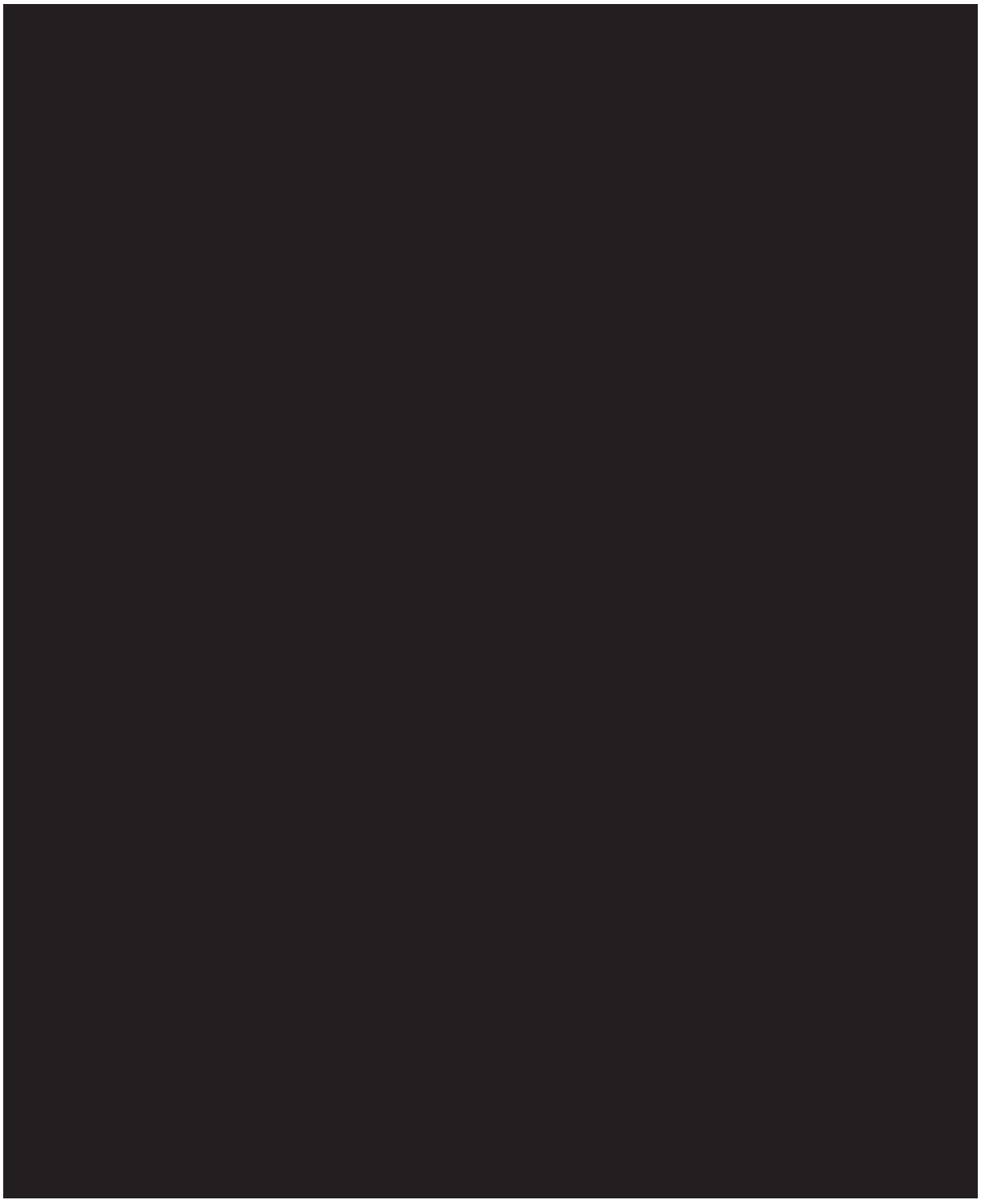
ACR50 and ACR70 are similarly defined with at least 50% and 70% improvement, respectively.

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 (PGA)
    - physician's global assessment of disease activity (PhGA)
    - patient's self-assessment of physical function (i.e., measured by Health Assessment Questionnaire (HAQ-DI score)
    - Acute-phase reactant value CRP

There are seven components to be evaluated to define an ACR response. Missing values for each component can occur due to a missed visit or due to dropout from the study. Depending on the pattern of the missing components, ACR responses may be or may not be determined using observed values only.

[redacted]



9.4.2 Joint Evaluation

Anatomical joints are evaluated for swelling and tenderness at every study visit. The 34 anatomical joints in Table 11 are assessed in this study for both the left and right side of the body.

Table 11. 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 assessed whether a particular joint was "tender or painful" where presence of tenderness was scored as "1" and the absence of tenderness was 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 Visual Analog Scale (VAS)

The subject will assess his/her disease activity for the past 24 hours using a Patient's Global Assessment of Disease VAS. The range is 0 to 100 mm with no activity being indicated by 0 and severe activity by 100.

9.4.4 Physician's Global Assessment of Disease Activity Visual Analog Scale (VAS)

The physician will assess Patient's disease activity at the time of visit using a Physician's Global Assessment of Disease VAS. The range is 0 to 100 mm with no activity being indicated by 0 and severe activity by 100.

9.4.5 Patient's Global Assessment of Pain

The subject will assess his/her pain in the previous week using a Patient's Global Assessment Pain VAS. The range is 0 to 100 mm with no pain being indicated by 0 and severe pain by 100.

9.4.6 Disease Activity Score (DAS28)

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

DAS28 (CRP) and DAS28 (ESR) can be calculated based on Tender Joint Count, Swollen Joint Count, Patient's Global Assessment of Disease Activity (PtGA) (in mm), and hsCRP (in mg/L) or ESR (mm/hr).

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

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

* 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 (CRP) equation is expressed as mg/hr.
» PtGA refers to the Patient's Global Assessment of Disease Activity.
where √ is square root and ln is natural log.

Table 12. 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		

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 Simplified Disease Activity Index (SDAI)

SDAI is a composite continuous index to assess disease activity based on TJC28, SJC28, Patient's Global Assessment of Disease Activity (PtGA) (in cm, 0 – 10), Physician's Global Assessment of Disease Activity (PhGA) (in cm, 0 – 10) and hsCRP (mg/dL). It can be derived as follows:

$$SDAI = TJC28 + SJC28 + PtGA\ (cm) + PhGA\ (cm) + hsCRP\ (mg/dL).$$

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

9.4.8 Clinical Disease Activity Index (CDAI)

CDAI is a composite continuous index to assess disease activity without using hsCRP measurement. It can be calculated based on TJC28, SJC28, Patient's Global Assessment

of Disease Activity (PtGA) (in cm, 0 – 10) and Physician's Global Assessment of Disease Activity (PhGA) (in cm, 0 – 10). It can be derived as follows:

$$CDAI = TJC28 + SJC28 + PtGA\ (cm) + PhGA\ (cm).$$

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

9.4.9 Clinical Remission (CR) and Low Disease Activity (LDA)

Clinical remission (CR) and low disease activity (LDA) based on DAS28 (CRP), DAS28(ESR), SDAI and CDAI are defined as follows:

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

9.4.10 ACR/EULAR Boolean Remission

ACR/EULAR Boolean remission is defined based on the following four criteria:

- Tender joint count ≤ 1 (based on 28 joints)
- Swollen joint count ≤ 1 (based on 28 joints)
- CRP ≤ 1 mg/dL
- Patient global assessment of disease activity ≤ 10 (mm)

All four criteria must be satisfied at a visit for a subject to be classified as achieving ACR/EULAR Boolean remission.

9.4.11 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. The higher the score, the more likely to associate with morbidity and mortality for the RA patient.

The maximum score for all the questions in each category is considered as the score for the category. The Standard disability index (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 of the eight disability categories there is an AIDS OR DEVICES companion variable(s) 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 disability 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 patient does not have scores for at least 6 categories.

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

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 pages. The first page measures 5 dimensions of the 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). The second page is an EQ Visual Analogue Scale (EQ VAS). EQ-5D health states, defined by the EQ-5D-5L descriptive system on the first page, may be converted into a single index value. The change from baseline of the index value and EQ VAS will be analyzed and reported. UK scoring algorithm will be used.

9.4.13 Form SF-36v2

The 36-Item Short Form, Version 2 (SF-36v2) Questionnaire with 4 week recall will be completed by the subject at Baseline, Weeks 4 and at study completion (Week 12 or at PD). The SF-36v2 health survey consists of 36 general health questions and this study is using the form for 4 weeks recall period (standard form). 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.

9.4.14 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Fatigue is one of the most frequent complaints of the elderly and is strongly associated with loss of independence and decreased physical activity and functional decline. One validated tool to measure fatigue is FACIT Fatigue Scale v4. The FACIT Fatigue Scale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. Each of the fatigue and impact of fatigue items are measured on a four point Likert scale. The FACIT Fatigue Scale is ranged from 0 to 52 and the higher the score, the better the quality of life.

Score for each item is calculated by either subtracted 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, multiplied by 13 and divided by the number of items answered. It is essentially a prorated subscale if there are missing values for some items. If less than or equal to 50% of the items are answered (e.g., 6 out of 13), the proration is not acceptable and the scale will not be computed.

9.4.15 Work Instability Scale for Rheumatoid Arthritis (RA-WIS)

The 23-item RA-WIS is a simple validated tool to evaluate work instability (the consequence of a mismatch between an individual's functional ability and their work

tasks). It can be self-administered by the patients. To calculate the RA-WIS scale, one can simply add up the number of "true" responses. If the scale is < 10, it means low risk and no action is needed. If the scale is between 10 and 17, it means medium risk and appropriate advice and information should be given. If the scale is > 17, it means high risk and it could warrant referral.

10.0 Safety Analysis

10.1 General Considerations

Safety analyses will be carried out using the Safety Analysis Set. There are two sets of planned safety analysis: safety analysis for Period 1, and long-term safety analysis.

Safety Analysis for Period 1

Standard safety analysis by the "as treated" treatment groups of Upadacitinib 7.5 mg QD, Upadacitinib 15 mg QD, Upadacitinib 30 mg QD, and combined placebo groups will be performed on safety data in Period 1. No protocol-defined treatment switching will occur prior to the end of Period 1.

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 group. Mean changes from baseline in all continuous laboratory parameters and vital signs variables at each visit will be summarized by "as treated" treatment group. 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 group. 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, mean change from baseline in

laboratory parameters and vital sign variables, 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 10.2.2.2). Listing of subjects with TEAEs by SOC and PT will be provided. Mean changes from baseline in all continuous laboratory parameters and vital signs variables at each visit will be summarized by "as treated" treatment group sequences defined as follows (as described in Section 10.3.3 and Section 10.4.3). 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:

1. Upadacitinib (ABT-494) 7.5 mg QD
2. Upadacitinib (ABT-494) 15 mg QD
3. Upadacitinib (ABT-494) 30 mg QD
4. Placebo →Upadacitinib (ABT-494) 7.5 mg QD
5. Placebo →Upadacitinib (ABT-494) 15 mg QD
6. Placebo →Upadacitinib (ABT-494) 30 mg QD

10.2 Analysis of Adverse Events

10.2.1 Treatment-Emergent 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 of the drug 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 19.0 or most up to date version. All adverse event tables will be sorted in alphabetical order by SOC and PT and descending percentages for each treatment group.

10.2.2 Analysis of Adverse Events for Period 1

10.2.2.1 Adverse Events Overview

The number and percentage of subjects experiencing TEAEs will be summarized by "as treated" treatment group and overall 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 AEs 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.

10.2.2.2 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing adverse events a will be tabulated by SOC and MedDRA PT by "as treated" treatment group and overall. 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 5% of subjects or more in any treatment group)
- TEAEs of special interest

Subjects reporting more than one adverse event for a given MedDRA preferred term 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.

10.2.2.3 TEAEs by Maximum Severity

TEAEs will also be summarized by maximum severity by "as treated" treatment group and overall. 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.

10.2.2.4 TEAEs by Relationship

TEAEs will also be summarized by relationship to Upadacitinib and Placebo, as assessed by the investigator, by "as treated" treatment group and overall. 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.

10.2.2.5 Frequent (≥ 5%) 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 5% of the subjects in any of the "as treated" treatment groups will be summarized by MedDRA PT in decreasing frequency separately.

10.2.2.6 Adverse Events of Special Interests

The Adverse Events of Special Interests (AESI) categories will be summarized and presented by "as treated" treatment group and overall using SOC and MedDRA PT. The AESI categories will be identified by the following search criteria per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs) in Table 13 below.

Table 13. 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"
Non-Melanoma Skin Cancer (NMSC)	SMQ	Broad	Skin Malignant tumours (Broad SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			Malignancy Narrow SMQ and 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		

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

10.2.3 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. Upadacitinib (ABT-494) 7.5 mg QD

   This includes AEs occurred under Upadacitinib 7.5 mg QD exposure from subjects starting on Upadacitinib 7.5 mg QD and subjects switching from placebo to Upadacitinib 7.5 mg QD.

2. Upadacitinib (ABT-494) 15 mg QD

   This includes AEs 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. Upadacitinib (ABT-494) 30 mg QD

   This includes AEs 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.

4. Placebo

10.2.3.1 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 and overall 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

For this calculation, 1 year will be considered to be 365.25 days. For each treatment group, the numerator of the overall 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 rates will be the total number of days exposed to study drug summed across all treated subjects divided by 365.25. Please refer to Section 8.0 for the calculation of study drug exposure. The AE rate per 100 patient-years of exposure will be calculated as ([numerator/denominator])*100. The number of AEs 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 and overall.

Additional AEs 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 rate per 100 patient-years between each Upadacitinib dose group and the combined placebo group.

10.2.3.2 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 events:

- 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
- TEAEs of special interest

For this calculation, 1 year will be considered to be 365.25 days. For each treatment group, the numerator of the overall rate, the SOC rate, or the PT rate, will be the total number of TEAEs reported overall, for the SOC, or for the PT, respectively; that is a subject can be counted more than once overall, for a SOC, and for a PT. For each treatment group, the denominator of the rates will be the total number of days exposed to study drug summed across all treated subjects divided by 365.25. Please refer to Section 8.0 for the calculation of study drug exposure. The AE rate per 100 patient-years of exposure will be calculated as [(numerator/denominator)]*100. The number of AEs reported (numerator), the total number of years of study drug exposure (denominator), and the AE rate per 100 patient-years will be presented overall, for each SOC, and for each PT for each treatment group.

10.2.3.3 Adverse Events of Special Interest Rates per 100 Patient-Years of Study Drug Exposure

The Adverse Events of Special Interest (AESI) categories will be summarized and presented for each treatment group and overall using SOC and MedDRA PT. The AESI categories will be identified per Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs).

For each treatment group, the Adverse Events of Special Interests (AESI) rate per 100 patient-years of exposure will be calculated overall, for each SOC and each PT, for each of the AESI listed in Section 10.2.2.6.

For this calculation, 1 year will be considered to be 365.25 days. For each treatment group, the numerator of the overall rate, the SOC rate, or the PT rate, will be the total number of TEAEs reported overall, for the SOC, or for the PT, respectively; that is a subject can be counted more than once overall, for a SOC, and for a PT. For each treatment group, the denominator of the rates will be the total number of days exposed to

study drug summed across all treated subjects divided by 365.25. Please refer to Section 8.0 for the calculation of study drug exposure. The AE rate per 100 patient-years of exposure will be calculated as [(numerator/denominator)]*100. The number of AEs reported (numerator), the total number of years of study drug exposure (denominator), and the AE rate per 100 patient-years will be presented overall, for each SOC, and for each PT for each treatment group.

10.2.3.4 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 14. List of Laboratory Variables

Laboratory Variables
Hematology
White Blood Cell (WBC) Count
Red Blood Cell (RBC) Count
Hemoglobin
Hematocrit
Platelets count
Neutrophils
Basophils
Eosinophils
Lymphocytes
Monocytes
Bands

Table 14. List of Laboratory Variables (Continued)

Laboratory Variables
Chemistry
Total Bilirubin
Alkaline Phosphatase (ALP)
Serum glutamic oxaloacetic transaminase (SGOT/AST)
Serum glutamic pyruvic transaminase (SGPT/ALT)
Total Protein
Albumin
Glucose
Triglycerides
Blood Urea Nitrogen (BUN)
Creatinine
Uric acid
Sodium
Potassium
Calcium
Inorganic Phosphorus
Creatine Phosphokinase (CPK)
Chloride
Bicarbonate
Cholesterol
LDL cholesterol
HDL cholesterol
International Normalized Ratio (INR) reflux only
Urinalysis
Specific Gravity
pH
Protein
Glucose
Ketones
Blood
Microscopic Examination (if needed)
Urobilinogen

Table 14. List of Laboratory Variables (Continued)

Laboratory Variables
Urinalysis (continued)
Bilirubin
Leukocytes
Nitrites
Other
hs-CRP
QuantiFERON-TB Gold
IgG and IgM
ESR

10.3.2 Analysis of Laboratory Data for Period 1

The laboratory data will be summarized by the "as treated" treatment groups (Upadacitinib 7.5 mg QD, Upadacitinib 15 mg QD, Upadacitinib 30 mg QD, and combined placebo groups) and overall.

10.3.2.1 Assessment of Mean Change from Baseline and Mean Percentage Change from Baseline in Clinical Laboratory Variables

Analyses of mean change from baseline in continuous hematology, chemistry, and urinalysis variables which are measured longitudinally will be performed by visits and by "as treated" treatment group. For each change from baseline analysis, the following summary statistics will be presented for each treatment group: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the changes from baseline. An ANOVA model with treatment as a factor will be used to test statistical significance for the change from baseline mean among different treatment groups.

In addition, similar analyses will be conducted for mean percentage change from baseline in hemoglobin, NK cells, LDL, HDL and triglycerides.

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 1, Grade 2, Grade 3, and Grade 4 according to OMERACT criteria (Rheumatology Common Toxicity Criteria v.2.0). For creatine phosphokinase, creatinine, NCI CTC criteria will be used.

For each laboratory variable, shift tables will be generated that cross tabulate the subjects' as deemed appropriate by "as treated" treatment group:

- Category of the baseline value versus category of the final value,
- Category of the baseline value versus maximum category.
- Category of the baseline value versus minimum category.

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 Variables

The criteria for potentially clinically significant laboratory values will be determined by OMERACT criteria of Grade 3 or 4. For creatine phosphokinase, creatinine, NCI CTC criteria will be used.

The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory values will be summarized by "as treated" treatment group and overall. Comparisons of the percentage of subjects experiencing a value meeting the criteria between treatment groups will be performed using Fisher's exact tests. Only p-values ≤ 0.100 when rounded to three digits will be presented.

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 (AT) 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 "as treated" treatment group:

- 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 Mean Change from Baseline and Mean Percentage Change from Baseline in Clinical Laboratory Variables

Analyses of mean change from baseline in continuous hematology, chemistry, and urinalysis variables which are measured longitudinally will be performed by visits and by "as treated" treatment group sequences as described in Section 10.1. For each change from baseline analysis, the following summary statistics will be presented for each treatment group: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the changes from baseline.

In addition, similar analyses will be conducted for mean percentage change from baseline in hemoglobin, NK cells, LDL, HDL and triglycerides.

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 switched treatment and experienced potentially clinical significant laboratory values under different treatment groups.

A listing of all subjects with any laboratory determination meeting OMERACT criteria of Grade 3 or 4 will be provided by Grade. For creatine phosphokinase, creatinine, NCI CTC criteria will be used. 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 similarly as described in Section 10.2.2:

- 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

A subject can be counted under different treatment groups if he/she switched treatment 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, respiratory rate, body temperature, and weight. The criteria for potentially clinically significant vital sign findings are presented in Table 15.

Table 15. 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
Respiratory Rate	Low	< 10 rpm
	High	> 24 rpm
Body temperature	High	> 39.0 degrees C (102.3 degrees F)
Weight	High	> 7% increase from baseline
	Low	> 7% decrease from baseline

10.4.2 Analysis of Vital Sign for Period 1

Analyses of mean change from baseline in continuous vital sign variables which are measured longitudinally will be performed by visits and by the "as treated" treatment groups of Upadacitinib 7.5 mg QD, Upadacitinib 15 mg QD, Upadacitinib 30 mg QD, and combined placebo groups. For each change from baseline analysis, the following summary statistics will be presented for each treatment group: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the changes from baseline. An ANOVA model with treatment as factor will be used to test statistical significance for the change from baseline mean among different treatment groups.

The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized by "as treated" treatment group and overall.

10.4.3 Analysis of Long Term Vital Sign

Analyses of mean change from baseline in continuous vital signs variables which are measured longitudinally will be performed by visits and by "as treated" treatment group sequences as described in Section 10.1. For each change from baseline analysis, the following summary statistics will be presented for each treatment group: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the changes from baseline.

Long Term Vital Sign 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 switched treatment and experienced potentially clinical significant laboratory values under different treatment groups.

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.

10.5 Analysis of ECG Parameters

10.5.1 Variables

ECG is collected at baseline visit, and Week 24/Prematurely discontinue. ECG findings will be summarized by treatment group for each parameter and visit.

11.0 Appendix

Appendix A OMERACT Criteria

Appendix A. OMERACT Criteria

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 Antirheumatic Therapies**				
	1 – Mild 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

A. Allergic/Immunologic (Continued)				
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
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. Induration/fibrosis/ Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and not disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms

E. Ear/Nose/Throat				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
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

F. Eye/Ophthalmologic (Continued)				
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
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

G. Gastrointestinal (Continued)				
G6. Haematochezia (rectal bleeding)	Haemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion > 3 – 4 units	> 4 units, hypotension, requiring hospitalization
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 (mmol/l)***	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 (mmol/l)***	-	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) ****	> ULN – 1.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 10.0 × ULN	> 10.0 × ULN
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 – 1.5 × Baseline; > ULN – 1.5 × ULN	> 1.5 – 3.0 × Baseline; > 1.5 – 3.0 × ULN	> 3.0 baseline; > 3.0 – 6.0 × ULN	> 6.0 × 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 – 1.5** × 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

*: in L11, 1.5 – 1.8 × ULN is changed to 1.4 – 1.8 × ULN.

**: in L14, 1.1 – 2.0 × ULN is changed to 1.1 – 1.5 × ULN.

***: in L3, L7 and L8, mg/dl is changed to mmol/l

****: NCI CTC grade

12.0 References

Not applicable.

Document Approval

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