1.0 Title Page

Statistical Analysis Plan

Study M14-465

A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib to Placebo and to Adalimumab in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who are on a Stable Background of Methotrexate (MTX) and Who Have an Inadequate Response to MTX (MTX-IR)

Date: 07 Dec 2017

Version 2.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the Data and Statistical Science Department for Upadacitinib Study M14-465. It provides details to further elaborate on statistical methods as outlined in the protocol.

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

4.0 Study Objectives, Design and Procedures

4.1 Study Objectives

Period 1

1. To compare the efficacy of Upadacitinib 15 mg once daily (QD) versus placebo, and versus adalimumab (ADA) for the treatment of signs and symptoms of rheumatoid arthritis (RA) in subjects with moderately to severely active RA who are on a stable background of methotrexate (MTX) and who have an inadequate response to MTX (MTX-IR).
2. To compare the efficacy of Upadacitinib 15 mg QD versus placebo for the prevention of structural progression in RA subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR).
3. To compare the safety and tolerability of Upadacitinib 15 mg QD versus placebo, and versus ADA in subjects with moderately to severely active RA subjects who are on a stable background of MTX and who have an inadequate response to MTX (MTX-IR).

Period 2

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

4.2 Overall Study Design and Plan

This is a Phase 3 multicenter study that includes two periods. Period 1 is a 48-week randomized, double blind, parallel-group, placebo-controlled and active comparator-controlled period designed to compare the safety and efficacy of Upadacitinib 15 mg QD versus placebo and versus ADA for the treatment of signs and symptoms of subjects with moderately to severely active RA who are on a stable dose of MTX and have an inadequate response to MTX (MTX-IR). Period 1 is also designed to compare the efficacy of Upadacitinib 15 mg QD versus placebo for the prevention of structural progression. Period 2 is a long-term extension to evaluate the safety, tolerability and efficacy of ABT-494 15 mg QD in subjects with RA who have completed Period 1.

The study is designed to enroll approximately 1500 subjects at approximately 510 study centers worldwide to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The study duration includes a 35-day screening period; a 48-week randomized, double-blind, parallel-group, placebo-controlled and active comparator-controlled treatment period (Period 1); a long-term extension period (blinded until the last subject completes Period 1) (up to 5 years) (Period 2); a 30-day follow-up period (call or visit); and a 70-day follow-up call.

Subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to one of three treatment groups:

- Group 1: Upadacitinib 15 mg QD (N = 600)
- Group 2: Placebo (N = 600)
- Group 3: ADA (40 mg every other week [eow]) (N = 300)

Subjects will receive both oral study drug QD (either Upadacitinib 15 mg or matching placebo) and subcutaneous study drug EOW (either ADA 40 mg or matching placebo) until the study is unblinded.

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

Subjects must have been on oral or parenteral MTX therapy for ≥ 3 months, on a stable MTX dose for ≥ 4 weeks prior to the first dose of study drug (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week), and must remain on a stable dose throughout the study; the MTX dose may be decreased only for safety reasons. In addition, all subjects should take a dietary supplement of oral folic acid (or equivalent) throughout study participation. Folic acid dosing and timing of regimen should be followed according to the Investigator's instructions. Starting at the Week 26 visit (after Week 26 assessments have been performed) and thereafter, initiation of or change in background RA medication(s) including, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol is allowed as per local label. Starting at Week 48 (after Week 48 assessments have been performed) and thereafter, initiation of or change in csDMARDs is allowed as per local label (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide, and restricted to concomitant use of up to 2 csDMARDs except the combination of MTX and leflunomide).

Starting at the Week 48 and thereafter, at least 20% improvement in BOTH TJC AND SJC compared to baseline is required to remain on study drug. Anyone who does not fulfill this criterion at 2 consecutive visits (starting at Week 48) must be discontinued from study drug.

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

discontinue that bDMARD due to intolerability (regardless of treatment duration) (for washout periods. These subjects will be equally stratified across all treatment groups. Subjects, who are considered bDMARD-inadequate responders (lack of efficacy), as determined by the Investigator, are not eligible.

Rescue therapy will be offered to subjects who meet the following criteria:

Placebo:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded Upadacitinib treatment.
- At Week 26, all remaining subjects will be switched to blinded Upadacitinib treatment regardless of clinical response.

ADA:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded Upadacitinib treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded Upadacitinib treatment.

Upadacitinib:

- Subjects who do not achieve a ≥ 20% improvement in TJC and SJC at Weeks 14, 18, or 22 compared to baseline will be switched to blinded ADA treatment.
- At Week 26, all remaining subjects who do not achieve LDA according to CDAI (LDA defined as CDAI ≤ 10) at Week 26 will be switched to blinded ADA treatment.

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

Each subject will undergo a maximum of 5 scheduled visits for x-ray examination of bilateral hands and feet during Period 1 (unless unscheduled repeat imaging is needed due to failure to meet the quality requirements) at Screening, Week 26, and Week 48/Premature Discontinuation. Subjects who are non-responders (defined as those not achieving ≥ 20% improvement in TJC and SJC criterion) at Week 14 and are switched to rescue therapy will have an x-ray examination at Week 14; in addition, subjects who prematurely discontinue from study drug or the study [redacted] will have an x-ray examination at the premature discontinuation timepoint (refer to protocol for additional details).

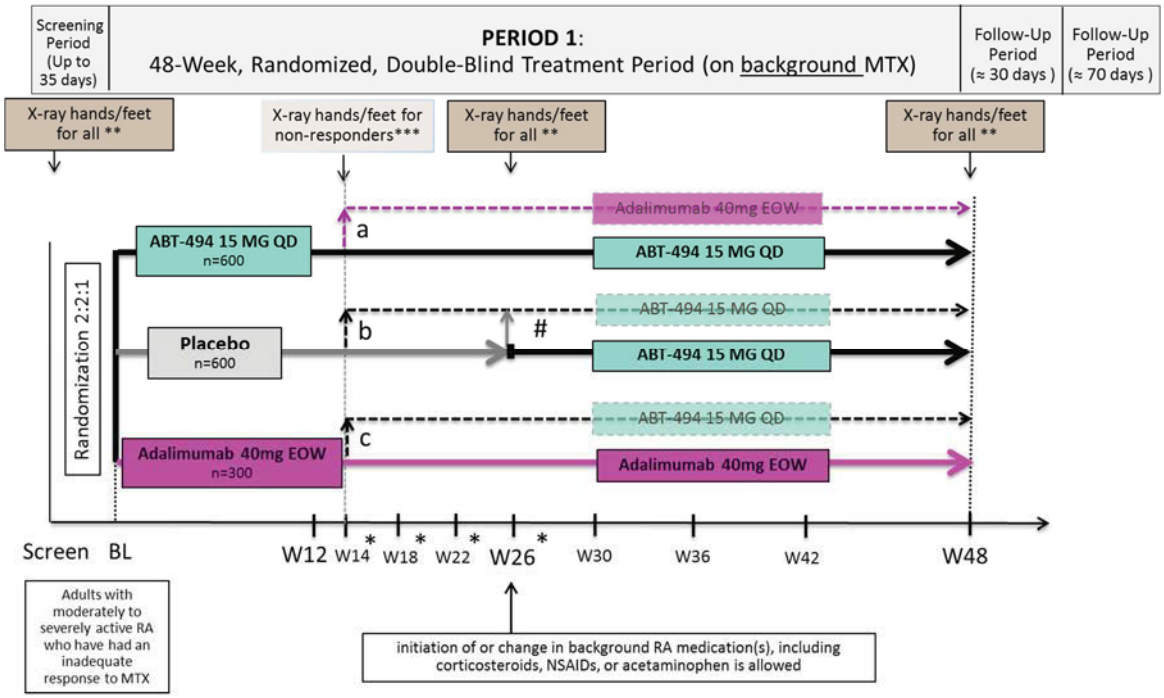
Joint x-rays will be sent to the central imaging vendor designated by the Sponsor. The x-rays will only be assessed by the imaging vendor for joint erosions and joint space narrowing, and will not be assessed for any other clinically significant findings that may impact a subject's health.

Subjects who complete the Week 48 visit (end of Period 1) will enter the long-term extension portion of the study, Period 2 (up to 5 years). Subjects will continue study treatment as assigned in Period 1. Subjects who are assigned to the upadacitinib 15 mg QD treatment group at the end of Period 1 will continue to receive upadacitinib 15 mg QD in a blinded manner. Subjects who are assigned to adalimumab 40 mg eow at the end of Period 1 will continue to receive adalimumab 40 mg eow in a blinded manner. When the last subject completes the last visit of Period 1 (Week 48), study drug assignment in both periods will be unblinded to the Sponsor and sites, and subjects will be dispensed study drug in an open-label fashion until the completion of Period 2.

Each subject will undergo an x-ray examination of bilateral hands and feet at Week 96/Premature Discontinuation (unless repeat testing is needed due to failure to meet the quality requirements) and every 96 weeks thereafter. Subjects who prematurely discontinue from the study will not need an x-ray of hands and feet if the previous x-ray was performed within the previous 24 weeks.

Schematics of Period 1 and Period 2 are shown in Figure 1 and Figure 2, respectively.

Figure 1. Period 1 Study Design



BL = baseline; EOW = every other week; MTX = methotrexate; QD = once daily; RA = rheumatoid arthritis; SJC = swollen joint count; TJC = tender joint count; W = week; NSAIDs = non-steroidal anti-inflammatory drugs

\# At W26, all placebo patients will be switched to upadacitinb 15 mg regardless of response.

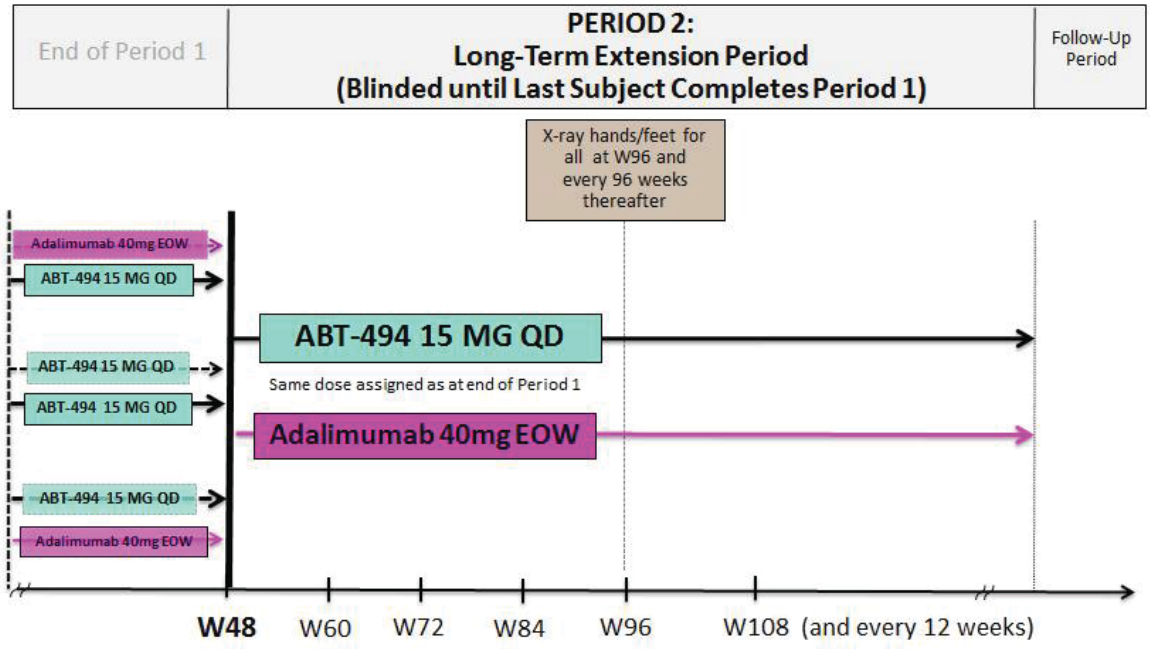
* Early escape for non-responders: (a) from upadactinib 15 mg QD to adalimumab at W14, W18, W22, or W26; (b) from placebo to ABT-494 15 mg QD at W14, W18, or W22; (c) from adalimumab to upadacitinib 15 mg QD at W14, W18, W22, or W26. Non-response at W14, W18, or W22 is defined as not achieving ≥ 20% improvement in TJC and SJC compared to baseline. Non-response at W26 is defined as not achieving LDA according to CDAI (LDA defined as CDAI ≤ 10).

** All patients will receive x-rays of hands and feet at Screening, W26, and W48.

*** X-rays at W14 will only be performed for non-responders.

Notes: The follow-up period is only for subjects who do not enter Period 2.

Figure 2. Period 2 Study Design



EOW = every other week; QD = once daily; W = week

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

Subjects that initially screen fail for the study are permitted to re-screen once following re-consent. For additional re-screening, AbbVie Therapeutic Area Medical Director approval is required. Lab values can be re-tested once during the re-screening period. 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), 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 (48-Week Randomized, Double-Blind Treatment Period)

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 48 Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the study and randomized to double-blind treatment. During this period of the study, subjects will visit the study site at Weeks 2, 4, 8, 12, 14, 18, 22, 26, 30, 36, 42, and 48. A ± 3 day window is permitted around scheduled study visits until Week 30 and ± 7 days for the remainder of the period. The last dose of oral study drug in Period 1 is taken the day prior to the Week 48 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 (Long-Term Extension Period [up to 5 Years])

Period 2 will begin at the Week 48 visit after all assessments have been completed. During Period 2, subjects will have a study visit at Weeks 60, 72, 84, 96, and every 12 weeks thereafter until completion of the study. A ± 7 day window is permitted around scheduled study visits. Starting at Week 48, subjects who failed to show at least 20% improvement in TJC and SJC compared to baseline at 2 consecutive visits will be discontinued from study drug treatment.

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

Subjects may discontinue study drug treatment, but choose to continue to participate in the study. Subjects who prematurely discontinue study drug should complete a Premature Discontinuation Visit (PD visit) as soon as possible, preferably within 2 weeks. Subjects should follow the regular visit schedule specified in the protocol, and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood sample collection for optional exploratory research and validation studies. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply for these subjects; this includes 20% TJC/SJC calculations at Weeks 14 – 22, and Week 48 and thereafter, as well as CDAI calculation at Week 26, if applicable. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

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

Subjects may withdraw from the study completely at any time (withdrawal of informed consent). If a subject prematurely discontinues study drug treatment AND study participation (withdrawal of consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, if the subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. For subjects on subcutaneous study drug, if the subject is willing, a 70-day follow-up phone call may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

Follow-Up Period

Subjects who have completed the last visit of Period 1 (Week 48) but decided not to participate in the extension Period 2 will have a follow-up visit approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AEs and to collect vital signs and clinical laboratory tests.

A 30-day follow-up visit will also occur for subjects who have completed Period 2.

A follow-up phone call will also occur 70 days after the last administration of subcutaneous study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The 70-day follow-up phone call will not be required for any subject that initiates commercial adalimumab.

The 30 day follow-up visit and 70 day follow-up call are not required for subjects who discontinued study drug and continued study participation with completion of at least one study visit approximately 30 days after last dose of oral or 70 days after last dose of subcutaneous study drug, respectively.

4.3 Sample Size

The planned total sample size of 1500 for this study (with a 2:2:1 randomization ratio) provides at least 90% power for a 22% difference in ACR20 response rate at Week 12 (assuming a placebo ACR20 response rate of 37%) at two-sided significance level of 0.05 and accounting for a 10% dropout rate. It will also provide at least 90% power for a 19.3% difference in CR (defined as DAS28(CRP) < 2.6) response rate at Week 12 (assuming a placebo CR response rate of 6.2%). With the given sample size, there is also approximately 90% power to detect a treatment difference of 0.39 in change from baseline in mTSS at Week 26 with a standard deviation of 2, at two-sided significance level of 0.05 and accounting for a 10% dropout rate. This sample size will also provide at least 90% power for testing non-inferiority of ABT-494 versus ADA in LDA (defined as DAS28(CRP) ≤ 3.2) or ACR50 response rate at Week 12 with a non-inferiority margin being 10%, assuming 35% and 40% LDA or ACR50 response rates for ADA and

upadacitinib, respectively. It will also provide at least 90% power in testing superiority of upadacitinib versus placebo for most of the ranked secondary endpoints, including change from baseline in DAS28 (CRP), change from baseline in HAQ-DI, ACR50 and ACR70 response rate, and SF-36 (PCS), at 2-sided significance level of 0.05 and accounting for a 10% dropout rate.

4.4 Interim Analysis and Date Base Lock

An unblinded analysis will be conducted after all subjects have completed Week 26 for the purpose of regulatory submission. Study sites and subjects will remain blinded for the duration of Period 1. Additional unblinded analyses may be conducted after the Week 26 unblinded analysis for regulatory purposes.

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 up to Week 12 in Period 1 of the

study. Additional analysis of the primary efficacy endpoint will be conducted on the Per Protocol analysis set, in order to evaluate the impact of major protocol deviations.

Major protocol deviations (ICH deviations and other clinically significant non-ICH deviations) will be identified prior to data base 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 analysis period.

5.2 Analysis Windows

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

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

Definition of Analysis Windows

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

visit closest to the target day will be used for analysis. If two visits are equidistant from the target day, then the later visit will be used for analysis.

The visit window and the target study day for each protocol-specified visit in Period 1 are displayed in Table 1, Table 2 and Table 3 (depending on the different visit schedules of different endpoints). Visit windows for protocol-specified visits in Period 2 are defined similarly.

Table 1. Analysis Windows for Efficacy Analysis for Period 1 (for ACR Components and Morning Stiffness) and 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	92
14	93	99	113
18	114	127	141
22	142	155	169
26	170	183	197
30	198	211	232
36	233	253	274
42	275	295	316
48	317	337	379

a. Day of first dose of study drug.

Table 2. Analysis Windows for Efficacy Analysis for Period 1 (for FACIT-F, EQ-5D-5L, SF-36, and RA-WIS)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
12	2	85	134
26	135	183	260
48	261	337	414

a. Day of first dose of study drug.

Table 3. Analysis Windows for Efficacy Analysis for Period 1 (for Radiographic Endpoints)

Protocol Specified Visit Week	Lower Bound	Target Day	Upper Bound
Baseline	–99	1[a]	1
14[b]	2	99	141
26	142	183	211
36[c]	212	253	295
48	296	337	379

a. Day of first dose of study drug.

b. Week 14 x-rays will be performed for all subjects who met the rescue criteria (i.e., non-responders) at Week 14.

c. Not protocol specified visit for x-ray assessment, but will be used to capture unscheduled or PD x-rays.

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

6.1 Demographics and Baseline Characteristics

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

Main Demographic and Baseline Characteristics

- Sex (male/female)
- Age (years)
- Age Categories (< 40, [40, 65), ≥ 65 years)
- Race (White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other)
- Geographic Region (North America, South/Central America, Western Europe, Eastern Europe, Asia, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Weight Categories (< 60 kg, ≥ 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 bDMARD use (Yes or No)
- Oral steroid use at baseline (yes, no)
- Oral steroid dose (prednisone equivalent) at baseline
- MTX dose at baseline
- Baseline MTX dose categories (< 15 mg/week or ≥ 15 mg/week)

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
- RF and Anti-CCP both positive vs. at least one negative
- RF and Anti-CCP both negative vs. at least one positive
- 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
- Radiographic related endpoints:
  - Modified Total Sharp Score (mTSS)
  - Joint erosion score
  - Joint space narrowing score

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)
- EQ-5D-5L
- 36-Item Short Form Health Survey (SF-36) Version 2: physical component summary, mental component summary and the 8 sub-domain scores

Clinical Tests at Screening

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

Immunization History

- BCG immunization
- Herpes Zoster immunization

- 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 groups 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 14 days of the last dose of study drug. This includes medications with a start date between first study drug administration and last study drug administration + 14 days, as well as, medications with a start date prior to first dose of study drug and which are ongoing after first dose of study drug. Medications taken on the day of the first dose of study drug are counted as concomitant medications.

The number and percentage of subjects who received a prior medication and the number and percentage of subjects who received a concomitant medication will be tabulated separately by the generic name assigned by the most current version of the World Health Organization (WHO) Drug Dictionary.

6.4 Protocol Deviations

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

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

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

7.0 Patient Disposition

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

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

This summary will be repeated by site.

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

Period 1

The numbers and percentages of subjects completed Period 1 and prematurely discontinued in Period 1will be summarized, separately by study drug and study participation completion/discontinuation, with the primary reason for discontinuation collected from CRF by the following categories:

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

Study participation completion/discontinuation will be summarized for Period 1 by randomized treatment group and by treatment group sequence, respectively.

Study drug completion/discontinuation will be summarized as follows:

- By randomized treatment group: number and percentage of completion by Week 14 and by Week 26, number/percentage and primary reason for discontinuation by Week 14 and between Week 14 to Week 26;
- By treatment group sequence: number and percentage of completion by Week 26 and by Period 1, number/percentage and primary reason for discontinuation between Week 14 to Week 26, and between Week 26 to end of Period 1.

Treatment group sequences are defined as:

1. Placebo → Upadacitinib 15 mg QD
2. ADA 40 mg EOW

3. ADA 40 mg EOW → Upadacitinib 15 mg QD
4. Upadacitinib 15 mg QD
5. Upadacitinib 15 mg QD → ADA 40 mg EOW

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.

Period 2

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

1. Upadacitinib 15 mg QD
2. ADA 40 mg EOW

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

For subjects who prematurely discontinued study drug or study participation, the primary reason 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

8.1 Study Drug Exposure

The duration of exposure to study drug will be summarized for the safety analysis set by the following groups. Subjects could switch to another treatment at Week 14 or later per study design. For subjects switching treatments, the exposure under the new study drug begins on the day when the new therapy is initiated, and the exposure under the previous study drug ends on the day before.

The duration of exposure to study drugs will be summarized by the following groups.

1. Placebo
2. ADA 40 mg EOW

   This includes ADA exposure from subjects starting on ADA 40 mg EOW and subjects who switched from Upadacitinib 15 mg QD to ADA 40 mg EOW.
3. Upadacitinib 15 mg QD

   This includes Upadacitinib 15 mg QD exposure from subjects starting on Upadacitinib 15 mg QD, subjects who switched from placebo to Upadacitinib 15 mg QD, and subjects who switched from ADA 40 mg EOW to Upadacitinib 15 mg QD.

The duration of exposure to study drug will be summarized for each group as specified above, with the number of subjects, mean, standard deviation, median, minimum and

maximum values. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following cumulative duration intervals.

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

8.2 Compliance

Study drug compliance for Upadacitinib/PBO and for ADA/PBO will be summarized separately for each treatment group up to Week 26. Upadacitinib/PBO compliance is defined as the number of Upadacitinib/PBO tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) during the subject's participation up to Week 26 divided by the number of days that the subject was in the Treatment Phase up to Week 26. ADA/PBO compliance is defined as the number of ADA injections administered during the subject's participation up to Week 26 divided by the number of injections planned during the subject's participation in the Treatment Phase up to Week 26.

9.0 Efficacy Analysis

9.1 General Considerations

There are three sets of planned efficacy analysis: efficacy analysis by Week 12, 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 by Week 12

Standard efficacy analysis by randomized treatment groups (placebo, ADA 40 mg EOW and Upadacitinib 15 mg QD) will be performed on efficacy data 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.

Efficacy Analysis for Period 1

For visits at Weeks 14, 18, 22, or 26, subjects may have switched to a treatment that is different from their originally randomized treatment group due to lack of efficacy. At Week 26, all remaining subjects in the original placebo group will be switched to blinded ABT-494 treatment regardless of clinical response. For treatment group comparison purposes, appropriate approaches will be applied to assessments that occur after the time of such treatment switching. For Week 26 reporting, this set of analyses will only be presented up to Week 26.

Long-Term Efficacy Analysis

Long-term efficacy analysis will be performed on As Observed data (defined in Section 9.1.2) by treatment group sequence as described below. There will be no statistical testing; only descriptive statistics and confidence intervals will be provided. For Week 26 reporting, this set of analyses will only be presented up to Week 48.

1. Placebo → Upadacitinib 15 mg QD
2. ADA 40 mg EOW
3. ADA 40 mg EOW → Upadacitinib 15 mg QD
4. Upadacitinib 15 mg QD
5. Upadacitinib 15 mg QD → ADA 40 mg EOW

9.1.2 Definitions of Missing Data Handling Approaches

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 schedules visit will be excluded from the OC analysis for that visit. In addition, OC will not include values after subject have switched study treatment or after premature discontinuation of study drug.

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 schedules 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.

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 are based on the assumption of data being missing at random and using the method of restrictive maximum likelihood (REML). [redacted]

Multiple Imputations (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]

Linear Extrapolation for Radiographic Data

For radiographic data (i.e., mTSS-based endpoints), linear extrapolation will be applied to subjects who were rescued or prematurely discontinued study drug, where the x-ray at the time point of interest after rescue or PD will be imputed assuming a linear relationship between baseline, the x-ray collected at rescue or PD, and the time point of interest.

To summarize the use of different missing data handling approaches in the analysis:

- For non-radiographic data: The NRI approach will serve as the primary analysis approach for key binary endpoints, while OC will be repeated as a sensitivity analysis. The MI approach will serve as the primary analysis approach for key continuous endpoints HAQ-DI and DAS28 at Week 12. The MMRM will serve as the primary analysis for other key continuous endpoints. The AO analysis will be performed for descriptive summary.
- For radiographic data: Analysis based on both linear extrapolation and AO will be conducted, and linear extrapolation results will be used for the purpose of multiplicity control.
- A missing not at random (MNAR) model that varies assumptions for the missing data in active treatment groups and placebo groups may be used as a sensitivity analysis for key continuous endpoints to account for potential deviation from the MAR assumption.

9.2 Efficacy Analysis by Week 12

9.2.1 Primary Efficacy Analysis

The primary endpoint for US/FDA regulatory purposes is the proportion of subjects achieving ACR20 response at Week 12. The primary endpoint for EU/EMA regulatory purposes is the proportion of subjects achieving CR based on DAS28(CRP) at Week 12. Analyses will be conducted separately for US/FDA regulatory purposes and EU/EMA regulatory purposes; for each set of analysis, only one primary endpoint is specified.

Analysis of the primary endpoint will be conducted on the FAS based on randomized treatment groups. Point estimate and 95% CI using normal approximation will be provided for the response rate for each randomized treatment group. Comparisons of the primary endpoint will be made between the Upadacitinib 15 mg QD group and the placebo group using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD 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 Observed Cases without any imputation as a sensitivity analysis. This will be conducted on the FAS based on randomized treatment groups.

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

9.2.3 Key Secondary Efficacy Analyses

Ranked key secondary endpoints (Upadacitinib versus placebo if not otherwise specified) for US/FDA regulatory purposes are:

1. Change from baseline in DAS28 (CRP) at Week 12;
2. Change from baseline in mTSS at Week 26;
3. Change from baseline in HAQ-DI at Week 12;
4. ACR50 response rate at Week 12 (non-inferiority of Upadacitinib vs ADA);
5. Change from baseline in SF-36 Physical Component Score (PCS) at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12;
7. Proportion of subjects achieving CR based on DAS28 (CRP) at Week 12;
8. Proportion of subjects achieving LDA based on CDAI ≤ 10 at Week 12;
9. Change from baseline in morning stiffness (duration) at Week 12;
10. Change from baseline in FACIT-F at Week 12;
11. ACR50 response rate at Week 12 (superiority of Upadacitinib vs ADA);
12. Change from baseline in patient's global assessment of pain at Week 12 (superiority of Upadacitinib vs ADA);

13. Change from baseline in HAQ-DI at Week 12 (superiority of Upadacitinib vs ADA).

Other key secondary endpoints (Upadacitinib versus placebo if not otherwise specified) for US/FDA purposes are:

1. ACR50 response rate at Week 12
2. ACR70 response rate at Week 12
3. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26

Ranked key secondary endpoints (Upadacitinib versus placebo if not otherwise specified) for EU/EMA regulatory purposes are:

1. Change from baseline in mTSS at Week 26;
2. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12;
3. Change from baseline in DAS28 (CRP) at Week 12;
4. Change from baseline in HAQ-DI at Week 12;
5. ACR20 response rate at Week 12;
6. Proportion of subjects achieving LDA based on DAS28 (CRP) ≤ 3.2 at Week 12 (non-inferiority of Upadacitinib vs ADA);
7. Change from baseline in SF-36 Physical Component Score (PCS) at Week 12;
8. Proportion of subjects achieving LDA based on CDAI ≤ 10 at Week 12;
9. Change from baseline in morning stiffness (duration) at Week 12;
10. Change from baseline in FACIT-F at Week 12;
11. Proportion of subjects with no radiographic progression (defined as change from baseline mTSS ≤ 0) at Week 26.

Other key secondary endpoints (Upadacitinib versus placebo if not otherwise specified) for EU/EMA purposes are:

1. ACR50 response rate at Week 12
2. ACR70 response rate at Week 12

For binary endpoints, frequencies and percentages will be reported for each treatment group. Similar analyses as for the primary endpoint will be conducted. Additionally, for ACR50 response rate at Week 12, analysis will be conducted to test the non-inferiority of Upadacitinib versus ADA using the 95% confidence interval of treatment difference against a non-inferiority margin of 10% for US/FDA regulatory purposes. Similar non-inferiority analysis will be conducted for LDA based on DAS28 (CRP) at Week 12 with a 10% margin for EU/EMA regulatory purposes. Superiority of Upadacitinib vs ADA will also be tested using the Cochran-Mantel-Haenszel test adjusting for stratification factor prior bDMARD use.

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 the Upadacitinib 15 mg group with the placebo group. For change from baseline in patient's global assessment of pain and change from baseline in HAQ-DI at Week 12, superiority of Upadacitinib vs ADA will also be tested.

Analyses for the mTSS-based key secondary endpoints are described in Section 9.3.2.

9.2.4 Exploratory Efficacy Analyses

Efficacy endpoints (Upadacitinib versus placebo and ADA) listed below will be summarized for all visits up to Week 12 by randomized treatment groups:

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

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

9.2.5 Handling of Multiplicity

In order to preserve Type I error, a step-down approach will be used to test the primary and ranked key secondary endpoints where statistical significance can be claimed for a lower ranked endpoint only if the previous endpoint in the sequence meets the requirements of significance. Specifically, the testing will utilize the endpoint sequence of primary endpoint followed by ranked key secondary endpoints in the order as specified in Section 9.2.3, using α of 0.05.

9.2.6 Efficacy Subgroup Analysis

The primary efficacy endpoint will be examined in the subgroups listed in Table 7 below. Treatment difference between the Upadacitinib 15 mg group and the 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., < 150 subjects), the subgroup analyses for that variable will not be presented.

Table 4. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	< 40, [40, 65), ≥ 65
Sex	Male or Female
Weight	< 60 kg or ≥ 60 kg
BMI	< 25 or ≥ 25
Race	White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other
Geographic Region	North America, South/Central America, Western Europe, Eastern Europe, Asia, Other
RA disease duration	< 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	Both Positive vs At Least One Negative
Baseline both RF negative and Anti-CCP negative	Both Negative vs At Least One Positive
Baseline DAS28[hsCRP)	< 5.1 or ≥ 5.1
Prior bDMARD use	Yes or No

9.2.7 Summary of Efficacy Analysis by Week 12

Table 5 below provides the overview of the efficacy analyses by Week 12 to be performed on different endpoints.

Table 5. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis by Week 12

Efficacy Variables	Analysis Method
Primary Variables	
• ACR20 response at Week 12[a] • CR based on DAS28(CRP) at Week 12[b]	• 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 Upadacitinib group and the 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 (Upadacitinib Versus Placebo if not Otherwise Specified)	
Binary Endpoints: • ACR50/70 response at Week 12 • ACR20 response at Week 12[b] • LDA as measured by DAS28(CRP) at Week 12 • CR as measured by DAS28(CRP) at Week 12[a] • LDA as measured by CDAI at Week 12 • ACR50 response at Week 12 (superiority of Upadacitinib vs ADA)[a]	• 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 Upadacitinib group and the comparator groups 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
Binary Endpoints (Non-inferiority of ABT-494 vs ADA): • ACR50 response rate at Week 12[a] • Proportion of subjects achieving LDA based on DAS28(CRP) ≤ 3.2 at Week 12[b]	• 95% confidence interval of treatment difference against a non-inferiority margin of 10%. • Imputation: NRI for primary analysis and OC for sensitivity analysis • Analysis Set: FAS

Table 5. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis by Week 12 (Continued)

Efficacy Variables	Analysis Method
Key Secondary Variables (Upadacitinib Versus Placebo if not Otherwise Specified) (continued)	
Continuous Endpoints: • Change from baseline in DAS28(CRP) at Week 12 • Change from baseline in HAQ-DI at Week 12 • Change from baseline in HAQ-DI at Week 12 (superiority of Upadacitinib vs ADA).[a]	• LS mean, and 95% CI within each treatment group and LS mean, 95% CI and p-values between Upadacitinib group and the comparator groups 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 morning stiffness (duration) • Change from baseline in FACIT-F • Change from baseline in patient's global assessment of pain at Week 12 (superiority of Upadacitinib vs ADA).[a]	• LS mean and 95% CI within each treatment group and LS mean, 95% CI and p-values between Upadacitinib group and the comparator groups 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 • LDA and CR based on DAS28(CRP), DAS28 (ESR), SDAI, and CDAI criteria • Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 and ≤ -0.22, respectively; • Boolean remission.	• 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 Upadacitinib group and the comparator groups 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 5. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis by Week 12 (Continued)

Efficacy Variables	Analysis Method
Additional Variables (Summarized at all Visits up to Week 12) (continued)	
Continuous Endpoints: • Change from baseline in individual ACR components • Change from baseline in DAS28 (CRP) and DAS28 (ESR) • Change from baseline in CDAI and SDAI • 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 Upadacitinib group and the comparator groups 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

a. US/FDA regulatory purposes.

b. EU/EMA regulatory purposes.

9.3 Efficacy Analysis for Period 1

Efficacy endpoints (Upadacitinib versus placebo and ADA) listed below will be summarized for all visits (that measurements are collected) in Period 1 by randomized treatment groups:

- Change from baseline in individual components of ACR response;
- ACR20/50/70 response rates;
- Change from baseline in DAS28(CRP) and DAS28 (ESR);
- Change from baseline in CDAI and SDAI;
- Proportion of subjects achieving LDA or CR based on DAS28 (CRP), DAS28 (ESR), Simplified Disease Activity Index (SDAI), and CDAI criteria (see below);
- Change from baseline in morning stiffness (severity and duration);

- Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3 and ≤ –0.22, respectively;
- ACR/EULAR Boolean remission;

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

Endpoints at Weeks 12, 26, and 48 are:

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

Endpoints at Weeks 26 and 48 are:

- Change from baseline in mTSS;
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS ≤ 0);
- Change from baseline in joint space narrowing score and joint erosion score.

9.3.1 Analysis of non-mTSS-Related Endpoints for Period 1

For continuous variables, statistical inference at each visit will be conducted using analysis of covariance (ANCOVA) with treatment and prior bDMARD use (Yes/No) as the fixed factor and the corresponding baseline value as the covariate. For subjects who meet the rescue criteria at either Week 14, 18, 22 or 26, data after rescue treatment switching will be overwritten by LOCF for the primary analysis. As observed (AO) data regardless of rescue treatment switching will also be summarized using descriptive statistics.

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 primary analysis, non-responder imputation will be used. In addition, subjects who meet the rescue criteria (based on joint improvement) at either Week 14, 18 or 22 will be treated as non-responders at visits after rescue treatment switching. For subjects who meet the rescue criteria (based on CDAI LDA) at Week 26, data after rescue treatment switching will be overwritten by the last response prior to rescue. As observed (AO) data regardless of rescue will also be summarized using frequencies and percentages.

Plots by randomized treatment group over time (corresponding to the primary analysis described in this section) will be provided for selected efficacy parameters including ACR20/50/70, LDA and CR by DAS28(CRP) and CDAI, and change from baseline in DAS28(CRP), HAQ-DI and pain.

For the analyses and plots described in this section, all three randomized treatment groups: Upadacitinib 15 mg QD, PBO, and ADA 40 mg EOW, will be present up to Week 26; and only two treatment groups: Upadacitinib 15 mg QD and ADA 40 mg EOW, will be present from Week 26 to Week 48.

For Week 26 reporting, this set of analysis will only be presented up to Week 26 (as all subjects would have had a chance to reach Week 26 but not all subjects would have had a chance to reach Week 48 by the Week 26 database lock).

9.3.2 Analysis of mTSS-Based Key Secondary Endpoints at Week 26

For mTSS-based key secondary endpoints at Week 26, both linear extrapolation and As Observed (AO) analyses will be conducted. Linear extrapolation results will be used for the purpose of multiplicity control.

According to protocol, subjects who are rescued to a different study drug at the Week 14 visit will have x-ray collected at that visit, and subjects who prematurely discontinue study drug [redacted] will have x-ray collected at the PD visit. All

subjects who remain in the study at Week 26 will also have x-rays collected at the Week 26 visit. Available x-ray data will be assigned to the following analysis windows as defined in Table 3: Baseline, Week 14, and Week 26.

In the linear extrapolation analysis, the Week 26 data will be imputed via linear extrapolation using x-ray from the baseline window and the Week 14 window for the following subjects: subjects rescued to a different study drug at Week 14, subjects who prematurely discontinued study drug [redacted] and subjects otherwise (i.e., not rescued to a different study drug at Week 14, not prematurely discontinued study drug [redacted] missing x-ray in the Week 26 window but have available x-ray in the Week 14 window.

In AO analysis, the observed Week 26 measurements will be used and attributed to the original randomized treatment groups regardless of treatment switching or study drug discontinuation.

For change from baseline in mTSS at Week 26, the point estimate and 95% CI will be reported for each randomized treatment group. Between-group comparisons for Upadacitinib 15 mg QD group and the placebo group will be performed using the analysis of covariance (ANCOVA) model with treatment and prior bDMARD use (Yes/No) as the fixed factors and the corresponding baseline value as the covariates. In the event that data severely deviates from the normal distribution, non-parametric analyses such as the Wilcoxon rank sum test may be considered for treatment comparison.

For proportion of subjects with no radiographic progression at Week 26, point estimate and 95% CI of the response rate for each randomized treatment group will be provided. Comparisons will be made between the Upadacitinib 15 mg QD group and the placebo group using the Cochran-Mantel-Haenszel test adjusting for prior bDMARD use (Yes/No). Point estimate, 95% CI and p-value for the treatment comparison will be presented.

9.3.3 Analyses of Additional mTSS-Related Endpoints for Period 1

For other mTSS-related endpoints at Week 26 and Week 48, analyses based on linear extrapolation and the As Observed (AO) analyses will be conducted. For Week 26 reporting, analysis of mTSS-related endpoints will only be presented up to Week 26.

For change from baseline in joint space narrowing score and joint erosion score at Week 26, linear extrapolation analysis and AO analysis will be performed similarly as described in Section 9.3.2.

According to protocol, subjects who are rescued to a different study drug at the Week 14 visit will have x-ray collected at that visit, and subjects who prematurely discontinue study drug [redacted] will have x-ray collected at the PD visit. All subjects who remain in the study at Week 26 will also have x-rays collected at the Week 26 visit, and all subjects who remain in the study at Week 48 will also have x-rays collected at the Week 48 visit. Available x-ray data will be assigned to the following analysis windows as defined in Table 3: Baseline, Week 14, Week 26, Week 36, and Week 48.

In the linear extrapolation analysis for Week 48 x-ray endpoints, the Week 48 data will be imputed via linear extrapolation for the following subjects: subjects who switched to a different study drug (by rescue at Week 14, 18, 22 or 26, or by switching from placebo to upadacitinib at Week 26), subjects who prematurely discontinued study drug [redacted] and subjects otherwise (i.e., not switched to a different study drug, not discontinued study drug [redacted] missing x-ray in the Week 48 window but have available post-baseline x-ray in an earlier analysis window. For those subjects who have switched study drug and/or prematurely discontinued study drug, x-ray data collected at treatment switching or at discontinuation of study drug will be used for extrapolation. For subjects otherwise missing observed x-ray in Week 48 window, available x-ray in the most recent analysis window (prior to the Week 48 window) will be used for extrapolation.

In the AO approach, the observed Week 48 measurements will be used and attributed to the original randomized treatment groups regardless of treatment switching or study drug discontinuation.

Similar statistical inference approach as described in Section 9.3.2 will be used.

9.3.4 Summary of Efficacy Analysis for Period 1

Table 6 below provides the overview of the efficacy analyses for Period 1 (including key secondary endpoints for mTSS) to be performed on different endpoints by randomized treatment group. For Week 26 reporting, this set of analysis will only be presented up to Week 26.

Table 6. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis for Period 1 (Including Key Secondary Endpoint for mTSS) (By Randomized Treatment Group)

Efficacy Variables	Analysis Method
Variables (Summarized at all Visits in Period 1)	
Binary Endpoints: • ACR20/50/70 response rate • Proportion of subjects achieving LDA and CR based on DAS28(CRP), DAS28 (ESR), SDAI, and CDAI criteria • Proportion of subjects with change from baseline in HAQ-DI ≤ –0.3 and ≤ –0.22, respectively; • Boolean remission; • Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS ≤ 0) at Weeks 26 and 48.	• 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 Upadacitinib group and the comparator groups using the Cochran-Mantel-Haenszel test adjusting forprior bDMARD use. The 95% CI will be based on normal approximation. • Plots by randomized treatment group over time • Imputation and treatment-switching handling for non-mTSS endpoints: NRI; AO for descriptive statistics • Imputation and treatment-switching handling for mTSS endpoints: linear extrapolation and AO • Analysis Set: FAS

Table 6. Summary of Efficacy Variables and Corresponding Analyses for Efficacy Analysis for Period 1 (Including Key Secondary Endpoint for mTSS) (By Randomized Treatment Group) (Continued)

Efficacy Variables	Analysis Method
Variables (Summarized at all Visits in Period 1) (continued)	
Continuous Endpoints: • Change from baseline in individual ACR components • Change from baseline in DAS28 (CRP) and DAS28 (ESR) • Change from baseline in CDAI and SDAI • Change from baseline in morning stiffness (severity and duration) • 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 • Change from baseline in modified Total Sharp Score (mTSS) at Week 26 and Week 48 • Change from baseline in JSN and Joint Erosion at Week 26 and Week 48	• LS mean and 95% CI within each treatment group and LS mean, 95% CI and p-values between Upadacitinib group and the comparator groups using ANCOVA model with treatment and prior bDMARD use as fixed factors and baseline value as covariate. Only nominal p-values will be provided. • Plots by randomized treatment group over time • Treatment-switching handling for non-mTSS endpoints: LOCF; AO for descriptive statistics. • Imputation and treatment-switching handling for mTSS endpoints: linear extrapolation and AO • Analysis Set: FAS

9.4 Long-Term Efficacy Analysis

Assessments to evaluate long-term efficacy will be analyzed for the following measures at each visit until completion of the study

- ACR20/50/70 response rates;
- Change from baseline in individual ACR components;
- Change from baseline in DAS28 (CRP);
- Change from baseline in DAS28 (ESR);
- Change from baseline in CDAI and SDAI;
- Change from baseline in morning stiffness (severity and duration);

- Proportion of subjects achieving LDA and the proportion of subjects achieving CR based on DAS28 (CRP), DAS28 (ESR), SDAI, and CDAI criteria;
- Proportion of subjects with change from baseline in HAQ-DI ≤ -0.3 and ≤ -0.22, respectively;
- Proportion of subjects with no concomitant corticosteroid use (among subjects with corticosteroid use at baseline);
- ACR/EULAR Boolean remission.

Additionally, assessment for the evaluation of radiographic changes in Period 2 will occur at Week 96 and every 96 weeks thereafter (or Premature Discontinuation visit):

- Change from baseline in modified Total Sharp Score (mTSS);
- Proportion of subjects with no radiographic progression (defined as change from baseline in mTSS of ≤ 0);
- Change from baseline in Radiographic joint space narrowing and joint erosion scores.

Descriptive statistics will be provided for each 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. Plots by treatment group sequence over time up to Week 48 will be provided.

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

For Week 26 reporting, long-term efficacy analysis will only be presented up to Week 48.

Table 7 below provides the overview of the long-term efficacy analyses to be performed on different endpoints.

Table 7. 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 change from baseline in HAQ-DI ≤ –0.3 and ≤ –0.22, respectively; • Proportion of subjects with no concomitant corticosteroid use (among subjects with corticosteroid use at baseline) • Proportion of subjects with no radiographic progression (defined as change from baseline mTSS of ≤ 0) by visit • Boolean remission	• Point estimate and 95% CI of the response rate for each treatment group sequence • Plot for each 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 CDAI and SDAI; • Change from baseline in morning stiffness (severity and duration) by visit • Change from baseline in EQ-5D-5L by visit • Change from baseline in RA-WIS by visit • Change from baseline in FACIT-F by visit • Change from baseline in SF-36 by visit • Change from baseline in mTSS by visit • Change from baseline in radiographic joint space narrowing and joint erosion scores by visit	• Point estimate, 95% CI of mean change from baseline together with SD, Min, Q1, Median, Q3 and Max for each treatment group sequence • Plot for each treatment group sequence over time • Imputation: AO • Analysis Set: FAS

9.5 Efficacy Variables Definitions and Conventions

9.5.1 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).

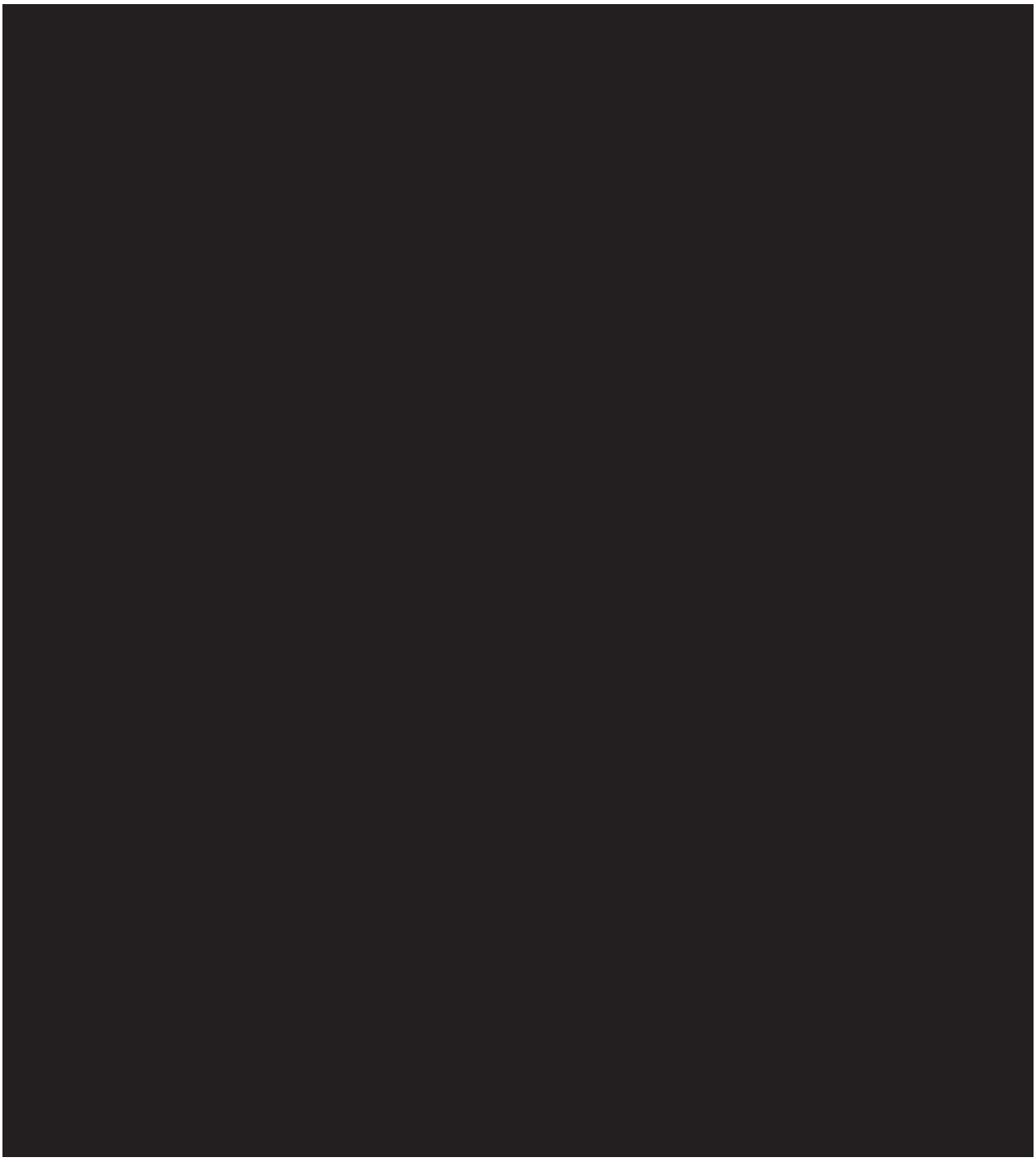
ACR50 and ACR70 are similarly defined with at least 50% and 70% improvement, respectively.

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

1. $\geq$ 20 % (50%, 70%) improvement from baseline in tender joint count (TJC68) and
2. $\geq$ 20 % (50%, 70%) improvement from baseline in swollen joint count (SJC66) and
3. $\geq$ 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]



9.5.2 Joint Evaluation

Anatomical joints are evaluated for swelling and tenderness at every study visit. The 34 anatomical joints in Table 8 are assessed in this study for both the left and right side of the body.

Table 8. 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.

9.5.3 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.

9.5.4 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.

9.5.5 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.

9.5.6 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 is, 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.

9.5.7 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 (in mm/hr).

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

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

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

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

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

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

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

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

Table 9. 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.

9.5.8 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.

9.5.9 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.

9.5.10 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

9.5.11 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.

9.5.12 Modified Total Sharp Score (mTSS)

The radiographic outcome will be assessed and scored according to Sharp's method (Van der Heijde modification) centrally by two qualified physicians/radiologists who will be blinded to the site number, subject number, treatment allocation, time sequence and clinical response.

Calculation of the Modified Total Sharp Score

To obtain the total mTSS score, scores for joint erosions and JSN in both the hands and feet will be added together.

The range of scores is summarized below.

	Hands	Feet	Total (Hands and Feet)
Joint Erosion Score Range	0 – 160	0 – 120	0 – 280
Joint Space Narrowing Range	0 – 120	0 – 48	0 – 168
mTSS Range for Joint Erosion and JSN	0 – 280	0 – 168	0 – 448

The following joints will be examined for assessing Joint Erosions:

Foot[a]		Hand[b]	
1st IP	1st IP	4th PIP	Navicular
1st MTP	1st MCP	4th MCP	Lunate
2nd MTP	2nd PIP	5th PIP	Radius
3rd MTP	2nd MCP	5th MCP	Ulnar
4th MTP	3rd PIP	1st MC	
5th MTP	3rd MCP	Multangular[c]	

a. IP: Inter-Phalangeal, MTP: Metatarso-Phalangeal.

b. IP: Inter-Phalangeal, PIP: Proximal Inter-Phalangeal, MCP: Metacarpophalangeal, MC: Metacarpal.

c. Trapezium/Trapezoid as read as one unit-Multangular.

The following joints will be examined for assessing Joint Space Narrowing:

Foot[a]		Hand[b]	
1st IP	1st MCP	4th MCP	MN
1st MTP	2nd PIP	5th PIP	CNL
2nd MTP	2nd MCP	5th MCP	RC
3rd MTP	3rd PIP	3rd CMC	
4th MTP	3rd MCP	4th CMC	
5th MTP	4th PIP	5th CMC	

a. IP: Inter-Phalangeal, MTP: Metatarso-Phalangeal.

b. PIP: Proximal Inter-Phalangeal, MCP: Metacarpo-Phalangeal, CMC: Carpo-Metcarpal, MN: Multangular-Navicular, CNL: Capitate-Navicular Lunate, RC: Radio-Carpal.

For each Joint and Bone assessed, scores range as follows:

- Joint Erosions: 0 – 5 (hands/wrists) or 0 – 10 (feet) to characterize the extent of erosions (where 0 denotes no erosion).
- Joint Space Narrowing: 0 – 4 to characterize the extent of Joint Space Narrowing (JSN) (where 0 denotes no narrowing).

Joint Erosion and JSN scores for each reader are calculated by taking the sum of the left and right joints as shown below.

$$\text{Erosion}_{\text{Reader i}} = \text{Erosion}_{\text{Left}} + \text{Erosion}_{\text{Right}}$$

$$\text{JSN}_{\text{Reader i}} = \text{JSN}_{\text{Left}} + \text{JSN}_{\text{Right}} \text{ for } i = 1, 2.$$

Thus, the maximum joint erosion score for all 32 joints in hands/wrists is 160. The maximum joint erosion score for all 12 joints in feet is 120. Thus, the total joint erosion score for hands/wrists and feet is 280.

The maximum score for JSN in all 30 hand/wrist joints is 120. The maximum score for JSN in all 12 feet joints is 48. Thus, the total JSN score for hand/wrist and feet is 168.

Since two independent readers evaluate each film, the mean score will be calculated for the two readers from the individual joint erosion and JSN scores as shown below:

$$\text{Joint Erosion} = \frac{\text{Erosion}_{\text{Reader1}} + \text{Erosion}_{\text{Reader2}}}{2}$$

$$\text{JSN} = \frac{\text{JSN}_{\text{Reader1}} + \text{JSN}_{\text{Reader2}}}{2}$$

The mTSS for each reader is defined as the sum of the joint erosion and JSN scores:

$$\text{TSS}_{\text{Reader i}} = \text{JointErosion}_{\text{Reader i}} + \text{JSN}_{\text{Reader i}} \text{ for i} = 1, 2.$$

The average modified TSS from the two readers will be used for all x-ray endpoint calculations.

$$TSS = \frac{TSS_{\text{Reader1}} + TSS_{\text{Reader2}}}{2}$$

[redacted]

[redacted]

Sensitivity analysis may be performed as needed.

Adjudication Process

Two reviewers will independently review the images. Adjudication will occur for all subjects with a discrepancy [redacted] between the two reviewers' mTSS change scores, in which case another reviewer, different from the reviewers who performed primary assessments, will make a third, independent assessment.

For the calculation of mTSS, the score of two closest reads (out of the two primary reviewers and the adjudicator) will be used. In the case of equal distance, the average of the three reads will be used.

9.5.13 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.

9.5.14 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, 8 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.

9.5.15 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 (4 = not at all to 0 = very much). 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.

9.5.16 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 three sets of planned safety analysis: safety analysis up to Week 14, safety analysis up to Week 26 censored at treatment switching, and long-term safety analysis. Missing safety data will not be imputed.

10.1.1 Safety Analysis up to Week 14

Standard safety analysis by the "as treated" treatment groups of placebo, ADA 40 mg EOW, Upadacitinib 15 mg QD groups will be performed on safety data up to Week 14. No protocol-defined treatment switching will occur prior to this time point.

The standard safety analyses will include reporting of adverse events (AEs), laboratory, and vital signs measurements. Frequency tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be provided by treatment 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.

10.1.2 Safety Analysis up to Week 26 Censored at Treatment Switching

Standard safety analysis by the "as treated" treatment groups of placebo, ADA 40 mg EOW, Upadacitinib 15 mg QD groups will be performed on safety data up to Week 26.

For subjects who are rescued to a different study drug prior to Week 26, safety data will be censored at the time of treatment switching.

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.

10.1.3 Long-Term Safety Analysis

Long-term safety analyses include reporting of AE rate adjusted by cumulative exposure, mean change from baseline in laboratory parameters and vital sign variables, and frequency 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 (i.e., exposed to) at the time of AE (treatment exposure for subjects switching treatments is described in Section 8.1). Listing of subjects with TEAEs by SOC and PT will be provided. 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.

For long-term analysis of TEAEs and potentially clinically significant laboratory or vital signs values, two sets of summaries will be provided, namely "summary based on all study drug exposure" and "summary based on long-term study drug."

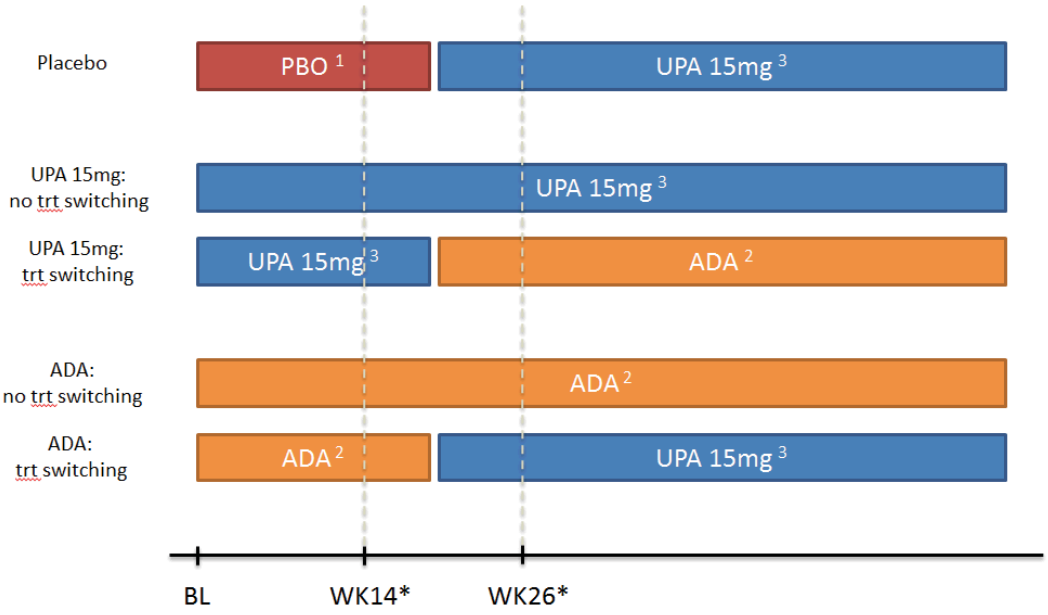
Summary based on all study drug exposure:

This summary will take into account safety data under the exposure of each study drug for each subject, i.e., an all-inclusive summary. The summary will be grouped by study drug as follows (and as illustrated in the figure below):

1. Placebo
2. Any ADA 40 mg EOW

   This includes ADA exposure from subjects starting on ADA 40 mg EOW and subjects rescued from Upadacitinib 15 mg QD to ADA 40 mg EOW
3. Any Upadacitinib 15 mg QD

   This includes Upadacitinib 15 mg QD exposure from subjects starting on Upadacitinib 15 mg QD, subjects rescued/switched from placebo to Upadacitinib 15 mg QD, and subjects rescued from ADA 40 mg EOW to Upadacitinib 15 mg QD



UPA = upadacitinib; ADA = adalimumab; PBO = placebo; WK = week; trt = treatment

* Treatment switching may occur at Week 14, 18, 22 or 26. Treatment switching in the graph is positioned between Week 14 and Week 26 for illustration purposes.

1. Belongs to group 1: Placebo.
2. Belongs to group 2: Any ADA 40 mg EOW.
3. Belongs to group 3: Any Upadacitinib 15 mg QD.

Summary based on long-term study drug:

"Summary based on long-term study drug" considers safety data from the study drug for which a subject will remain on long-term for the rest of the study. For subjects who did not switch treatment during the study, all safety data under the original study drug will be summarized. For subjects who switched treatment during the study, safety data under the study drug that they switched to (i.e., the second study drug) will be summarized; in this case, safety data from the first study drug is only short-term and therefore will not be included in this summary. The treatment groups for this summary are as follows (and as illustrated in the figure below):

1. Upadacitinib 15 mg QD, switched from Placebo

This includes Upadacitinib 15 mg QD exposure from subjects who switched from placebo to Upadacitinib 15 mg QD (either due to rescue treatment switch or systematic switch at Week 26)

2. Upadacitinib 15 mg QD, no treatment switching

   This includes Upadacitinib 15 mg QD exposure from subjects starting on Upadacitinib 15 mg QD and who did not switch study treatment due to rescue

3. ADA 40 mg EOW, no treatment switching

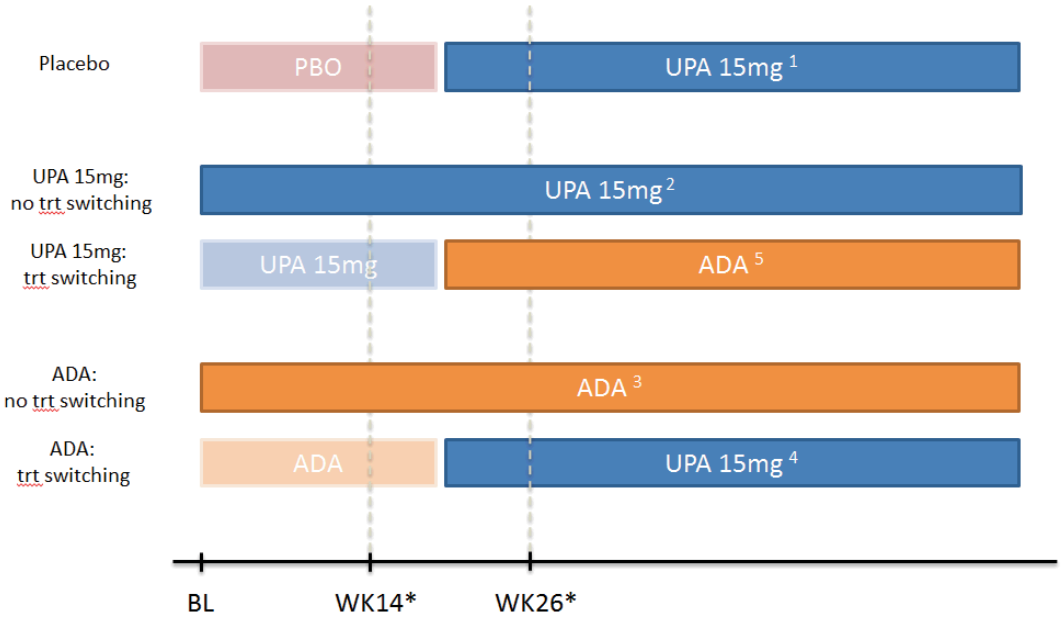
   This includes ADA 40 mg EOW exposure from subjects starting on ADA 40 mg EOW and who did not switch study treatment due to rescue

4. Upadacitinib 15 mg QD, switched from ADA

   This includes Upadacitinib 15 mg QD exposure from subjects who switched from ADA 40 mg EOW to Upadacitinib 15 mg QD

5. ADA 40 mg EOW, switched from Upadacitinib

   This includes ADA 40 mg EOW exposure from subjects who switched from Upadacitinib 15 mg QD to ADA 40 mg EOW



UPA = upadacitinib; ADA = adalimumab; PBO = placebo; WK = week; trt = treatment

* Treatment switching may occur at Week 14, 18, 22 or 26. Treatment switching in the graph is positioned between Week 14 and Week 26 for illustration purposes.

1. Belongs to group 1: Upadacitinib 15 mg QD, switched from Placebo.
2. Belongs to group 2: Upadacitinib 15 mg QD, no treatment switching.
3. Belongs to group 3: ADA 40 mg EOW, no treatment switching.
4. Belongs to group 4: Upadacitinib 15 mg QD, switched from ADA.
5. Belongs to group 5: ADA 40 mg EOW, switched from Upadacitinib.

In addition to the analyses described above, 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:

1. Placebo → Upadacitinib 15 mg QD
2. ADA 40 mg EOW
3. ADA 40 mg EOW → Upadacitinib 15 mg QD
4. Upadacitinib 15 mg QD
5. Upadacitinib 15 mg QD → ADA 40 mg EOW

10.2 Analysis of Adverse Events

A treatment-emergent Adverse Event (TEAE) is defined as an adverse event with an onset date that is after the first dose of study drug, and no more than 30 days or 5 half-lives of the drug, whichever is larger, after the last dose of study drug. Specifically, 30 days will be used for Upadacitinib and placebo, and 70 days will be used for ADA.

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.

10.2.1 Analysis of Short-Term Adverse Events

Two sets of analysis will be conducted for short-term adverse events, namely "safety analysis up to Week 14" and "safety analysis up to Week 26 censored at treatment switching" as outlined in Section 10.1.1 and Section 10.1.2. Adverse events will be summarized by frequency and percentages by "as treated" treatment groups of placebo, ADA 40 mg EOW and Upadacitinib 15 mg QD.

10.2.1.1 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 percentages.

As a sensitivity analysis, the AE overview summary will be repeated by randomized treatment groups. In this summary, all AEs with an onset date after the first dose of study drug will be included, regardless of whether the AE occurred more than 30 days (or 70 days) after the last dose of study drug.

10.2.1.2 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 groups 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 2% of subjects or more in any treatment group)

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.

As a sensitivity analysis, the AE summary by SOC and PT will be repeated by randomized treatment groups. In this summary, all AEs with an onset date after the first dose of study drug will be included, regardless of whether the AE occurred more than 30 days (or 70 days) after the last dose of study drug.

10.2.1.3 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.

10.2.1.4 TEAEs by Maximum Relationship

TEAEs will also be summarized by maximum 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.

10.2.1.5 Frequent (≥ 2%) Adverse Events and Reasonably Possibly Related Adverse Events by System Organ Class and Preferred Term

TEAEs and reasonably possibly related AEs occurring for more than 2% of the subjects in any of the "as treated" treatment groups will be summarized by MedDRA PT in decreasing frequency separately.

10.2.1.6 Adverse Events of Special Interest

The Adverse Events of Special Interest (AESI) categories will be summarized and presented by "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 10 below.

Table 10. 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"
Possible Malignancy	SMQ	Narrow	"Malignancies"
Malignancy	SMQ		"Malignant tumours"
Non-Melanoma Skin Cancer (NMSC)	SMQ	Broad	Skin Malignant tumours (Broad SMQ) removing Melanoma CMQ
Malignancy excluding NMSC			"Malignant tumours" SMQ removing NMSC output
Lymphoma	SMQ		"Malignant Lymphomas"
Hepatic Disorder	SMQ	Narrow	"Drug Related Hepatic Disorders"
Gastrointestinal Perforations	SMQ	Narrow	"Gastrointestinal Perforation"
Anemia	CMQ		"Non-Hemolytic and Non-Aplastic Anemias"
Neutropenia	CMQ		"Hematological Toxicity – Neutropenia"
Lymphopenia	CMQ		"Hematological Toxicity – Lymphopenia (Veliparib Product Specific)"
Herpes Zoster	CMQ		"Herpes Zoster"
Creatine Phosphokinase (CPK) Elevation	PT		Search only for the PT of "Blood creatine phosphokinase increased"
Renal Dysfunction	SMQ	Narrow	"Acute Renal, Failure"
Tuberculosis	CMQ		"Tuberculosis"
Adjudicated Cardiovascular Events	Output from CAC		
MACE*			
Undetermined/Unknown Cause of Deaths			

Table 10. AESI for Upadacitinib with SMQs/CMQs/PTs Searches (Continued)

AESI	Type of MedDRA Query	Broad or Narrow Search	SMQ/CMQ Search Criteria
Other Cardiovascular events			
Venous Thromboembolic Events**			
Other Venous Thrombosis			
Arterial Thromboembolic Events (non-cardiac, non-neurologic)			

* MACE; Major Adverse Cardiovascular Events, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

** Venous thromboembolic events (VTE) include deep vein thrombosis (DVT) and pulmonary embolism (PE).

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

10.2.2 Analysis of Long-Term Adverse Event Rates

Long-term adverse event rates will be analyzed using event rates adjusted by cumulative exposure and will be based on the actual treatment received at the time of AE occurrence. Two sets of summaries, "summary based on all study drug exposure" and "summary based on long-term study drug," respectively, will be provided following the treatment groups as described in Section 10.1.3.

10.2.2.1 Overview of Adverse Events Rates per 100 Patient-Years of Study Drug Exposure

An overview of AEs per 100 patient-years of study exposure will be presented by treatment group 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, one 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 6.0 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 rates per 100 patient-years.

10.2.2.2 Adverse Events Rates per 100 Patient-Years of Study Drug Exposure by SOC and PT

For each treatment group, the TEAE rate per 100 patient-years of exposure will be calculated overall, for each SOC and each PT, for each of the following 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

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 6.0 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.

10.2.2.3 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 Interest (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 10.2.1.6.

For this calculation, one 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 6.0 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.

10.2.2.4 Listing of Serious Adverse Events (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All serious adverse events (SAEs), deaths, and adverse events leading to discontinuation of study drug will be listed.

10.3 Analysis of Laboratory Data

10.3.1 Variables and Units

All laboratory parameters to be collected in this study are listed below. Laboratory parameters will be reported using the standard international (SI) units.

Table 11. 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
Chemistry
Total Bilirubin
Alkaline Phosphatase (ALP)
Serum glutamic oxaloacetic transaminase/aspartate aminotransferase (SGOT/AST)
Serum glutamic pyruvic transaminase/alanine aminotransferase (SGPT/ALT)
Total Protein
Albumin
Glucose
Triglycerides
Blood Urea Nitrogen (BUN)
Creatinine
Uric acid
Sodium
Potassium
Calcium
Inorganic Phosphorus
Creatine Phosphokinase (CPK)
Chloride
Bicarbonate

Table 11. List of Laboratory Variables (Continued)

Laboratory Variables
Chemistry (continued)
Cholesterol (TC)
LDL cholesterol (LDL-C)
HDL cholesterol (HDL-C)
LDL-C/HDL-C ratio
TC/HDL-C ratio
Urinalysis
Specific Gravity
pH
Protein
Glucose
Ketones
Blood
Microscopic Examination (if needed)
Urobilinogen
Bilirubin
Leukocytes
Nitrites
Other
hs-CRP
QuantiFERON-TB Gold[a]
IgG and IgM
ESR

a. For annual follow-up QFT is captured only for those with negative QFT at Screening.

10.3.2 Analysis of Short-Term Laboratory Data

Two sets of analysis will be conducted for short-term laboratory data (unless otherwise specified), namely "safety analysis up to Week 14" and "safety analysis up to Week 26 censored at treatment switching" as outlined in Section 10.1.1 and Section 10.1.2. Data

will be summarized by "as treated" treatment group (placebo, ADA 40 mg EOW, Upadacitinib 15 mg QD).

10.3.2.1 Assessment of Mean 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.

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

Analysis of mean change and mean percent change by visit will only be provided for "safety analysis up to Week 26 censored at treatment switching." Analysis will not be repeated for "safety analysis up to Week 14," because it will be a subset of the former.

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 and 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 and 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.

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 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 at the end of Section 10.1.3. 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. Plots of mean change from baseline by treatment group sequences over time up to Week 48 may be provided for key lab parameters.

In addition, similar analyses will be performed for percentage change from baseline in hemoglobin, LDL-C, HDL-C and triglycerides.

10.3.3.2 Assessment of Potentially Clinically 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 accrual treatment received at the time of the event occurrence. Two sets of

summaries, namely "summary based on all study drug exposure" and "summary based on long-term study drug," will be provided following the treatment groups as described in Section 10.1.3 (similar to the analysis of long-term adverse events). In the "summary based on all study drug exposure," a subject can contribute to two treatment groups if he/she switched treatment. In the "summary based on long-term study drug," a subject will only contribute to one treatment group.

In the evaluation of potentially clinically significant laboratory values, the baseline value will be determined by the last non-missing measurement recorded on or before the date of the first dose of study drug in the corresponding treatment group (which may be different than the first dose of study drug received in the study). For example, for a subject who started on placebo and switched to Upadacitinib 15 mg QD, lab values under Upadacitinib 15 mg QD exposure would be evaluated against the baseline value defined as the last non-missing measurement recorded on or before the date of the first dose of Upadacitinib 15 mg QD.

A listing of all subjects with any laboratory determination meeting OMERACT criteria of Grade 3 or 4 will be provided by Grade. For creatine phosphokinase and 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. Two sets of summaries, namely "summary based on all study drug exposure" and "summary based on long-term study drug," will be provided, similarly as described in Section 10.3.3.2.

- ALT $\geq 3 \times$ ULN
- ALT $\geq 5 \times$ ULN
- ALT $\geq 10 \times$ 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 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 12.

Table 12. 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 Short-Term Vital Signs

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 group. Analysis will be conducted for "safety analysis up to Week 26 censored at treatment switching." 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.

The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized by "as treated" treatment group for "safety analysis up to Week 14" and "safety analysis up to Week 26 censored at treatment switching," respectively.

10.4.3 Analysis of Long-Term Vital Signs

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 sequence as described at the end of Section 10.1.3. 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. Two sets of summaries, namely "summary based on all study drug exposure" and "summary based on long-term study drug," will be provided, similarly as described in Section 10.3.3.2. In the evaluation of potentially clinically significant vital sign values, the baseline value will be determined by the last non-missing measurement recorded on or before the date of the first dose of study drug in the corresponding treatment group, similarly as described in Section 10.3.3.2.

A listing of all subjects with any vital sign values meeting the criteria for potentially clinically significant vital signs will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

11.0 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
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
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
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
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
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
L9. CPK (also if polymyositis-disease	1.2 – 1.9 × ULN	2.0 – 4.0 × ULN	4.0 × ULN with weakness but without life-threatening signs or symptoms	> 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening
L10. Serum uric acid	1.2 – 1.6 × ULN	1.7 – 2.9 × ULN	3.0 – 5.0 × ULN or gout	NA
L11. Creatinine (mg/dl)	1.1 – 1.3 × ULN	1.4* – 1.8 × ULN	1.9 – 3.0 × ULN	> 3.0 × ULN
L12. SGOT (AST)	1.2 – 1.5 × ULN	1.6 – 3.0 × ULN	3.1 – 8.0 × ULN	> 8.0 × ULN
L13. SGPT (ALT)	1.2 – 1.5 × ULN	1.6 – 3.0 × ULN	3.0 – 8.0 × ULN	> 8.0 × ULN
L14. Alkaline phosphatase	1.1 – 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.

**** For CPK and Creatinine NCI CTC grading will be used. For CPK therefore the following gradings apply: Grade 1: > ULN – 2.5 × ULN; Grade 2: > 2.5 – 5.0 × ULN; Grade 3: > 5.0 – 10.0 × ULN; Grade 4: > 10.0 × ULN; For Creatinine the following gradings apply: Grade 1: > 1 – 1.5 × Baseline; > ULN – 1.5 × ULN; Grade 2: > 1.5 – 3.0 × Baseline; > 1.5 – 3.0 × ULN; Grade 3: > 3.0 baseline; > 3.0 – 6.0 × ULN; Grade 4: > 6.0 × ULN.

Document Approval

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