1.0 Title Page

Clinical Study Protocol M13-538

Phase 2 Study, Multicenter, Open-Label Extension (OLE) Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial (RCT) with Upadacitinib (ABT-494)

Incorporating Administrative Changes 1 and 2 and Amendments 0.01, 0.02, 0.03, 1, 2, 3, 4, 5 and 6

AbbVie Investigational Product:	Upadacitinib
Date:	01 December 2020
Development Phase:	2
Study Design:	This is a multicenter open-label study.
EudraCT Number:	2013-003530-33
Investigators:	Multicenter Trial (Investigator information is on file at AbbVie)
Sponsor:	AbbVie Inc.* 1 North Waukegan Road North Chicago, IL 60064
Sponsor/Emergency Medical Contact:	[redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: Mobile: Email: [redacted] EMERGENCY 24 hour Number: +1 973-784-6402

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

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	30 September 2013
Administrative Change 1	28 March 2014
Amendment 0.01 (UK Only)	23 July 2014
Administrative Change 0.01 (Romania Only)	19 August 2014
Amendment 1	19 November 2014
Amendment 0.02 (UK Only)	18 December 2014
Amendment 2	12 January 2016
Amendment 0.03 (UK Only)	25 February 2016
Administrative Change 2	10 March 2017
Amendment 3	10 November 2017
Amendment 4	13 February 2019
Amendment 5	09 November 2019

The purpose of this amendment is to incorporate changes summarized below:

- Apply administrative changes throughout protocol

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

  Rationale: *Revised to update the sponsor Emergency/Medical Contact for the study.*
- Update Section 1.2, Synopsis

  Rationale: *Revised to be consistent with current Amendment revisions.*
- Update Section 1.3, List of Abbreviations and Definition of Terms

  Rationale: *Updated to include new terms, Coronavirus Disease – 2019 (COVID-19) and Direct-to-Patient (DTP)*
- Update Section 3.2, Benefits and Risks

Rationale: *Revised to include the evaluation of the benefit and risk to subjects participating in the study relative to COVID-19.*

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

  Rationale: *Added provisions for virtual or alternative locations for study visits in the event of a pandemic situation like COVID-19 or any state of emergency (e.g., natural disaster, conflict/combat) to ensure the safety of subjects and site staff, while maintaining the integrity of the study.*

  Updated to allow the 30-day follow up visit to be a phone call or site visit.

- Update Section 5.2.3.1, Prohibited Therapy

  Rationale: *Revised Table 1 to update the list of examples of commonly used strong cytochrome 3A inducers.*

- Update Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart

  Rationale: *Added clarifications on study activities that can be performed by phone/video conference or at local clinic/hospital/laboratory or through the optional home healthcare service in the event study visits are impacted by any state of emergency or pandemic situation like COVID-19 to ensure subjects' safety and study continuation, as permitted by IRB/IEC.*

  Added the footnote "q" to the Table 2 "Study Activities" to clarify that the 30-day follow up visit can be a phone call or site visit.

- Update Section 5.3.1.1, Study Procedures
  - Patient's Global Assessment of Disease Activity Visual Analog Scale (VAS), Patient's Assessment of Pain Visual Analog Scale (VAS), Health Outcomes Questionnaires.

    Specified that these questionnaires are not eligible for completion by virtual interview in the event that the subject cannot perform an onsite visit due to a pandemic or state of emergency and will be completed by the patient at the next earliest feasible subject's visit
  - Physical Examination

    Added provision allowing the complete physical examination to be performed at the next earliest feasible visit.

- Physician Global Assessment of Disease Activity Visual Analog Scale (VAS)

  Specified that Physician Global Assessment of Disease Activity is not eligible for completion by virtual interview in the event that the subject cannot perform an onsite visit due to a pandemic or state of emergency and will be completed by the physician at the next earliest feasible subject's visit.

- Tender Joint Count (TJC) and Swollen Joint Count (SJC) Assessments

  Added provision allowing the TJC and SJC to be performed at the next earliest feasible visit by the independent joint assessor, if possible.

- Pregnancy Test

  Added provision allowing the urine pregnancy test to be performed at a local laboratory or at home.

- TB (tuberculosis) Testing/Chest X-ray (CXR)

  Specified that chest X-rays can be performed at the next earliest feasible visit unless the Investigator has determined that a CXR is required to ensure that it is safe to continue study drug administration (e.g., subjects with seroconversion on an annual TB test). In this case, the Investigator should contact the AbbVie Therapeutic Area Medical Director (TA MD) to determine if the subject may continue on study drug and CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

- 12-Lead Electrocardiogram (ECG)

  Specified that the 12-Lead ECG can be performed at the next earliest feasible visit unless the Investigator has determined that an ECG is required to ensure that it is safe to continue study drug administration. In this case, the ECG should be performed as soon as restrictions allow at the study site or local hospital/facility.

- Clinical Laboratory Tests

  Added provision allowing the laboratory testing at an alternate local facility, in the event that a state of emergency or pandemic prevents the subject from performing the central laboratory tests and added the

requirements to allow the study drug dispensation when laboratory tests are performed at a local laboratory.

- Study Drug Dispensing, Dosing and Compliance

  Added provision allowing Direct-to-Patient (DTP) shipment of study drug and study ancillaries due to state of emergency or pandemic situations.

- New Section: Optional Home Healthcare Service Due to State of Emergency or Pandemic Situation like COVID-19

  Added home healthcare visits as an option in case a study visit on site cannot be performed due to state of emergency or pandemic-related reasons.

Rationale: *To modify study visits and protocol-specific procedures impacted by the COVID-19 or any pandemic/state of emergency as necessary, to ensure the safety of subjects/site staff and study continuation including alternative locations for data collection, as permitted by IRB/IEC.*

- Update Section 5.4.1, Discontinuation of Individual Subjects and Section 6.10 Toxicity Management

  Rationale: *Revised to clarify that subjects will have to discontinue study drug treatment immediately if they develop a gastrointestinal perforation with the exception of appendicitis or mechanical injury to be consistent with the Section 6.10 "Toxicity Management."*

  Clarified that the state of emergency and pandemic-related restrictions may allow mitigation strategies to ensure subject safety and continuity of care as an alternative to study discontinuation/study drug discontinuation and that the AbbVie TAMD should be contacted before discontinuing a subject to ensure all acceptable mitigation steps have been explored.

- Update Section 5.5.1, Treatments Administered

  Rationale: *Added specifications in order to provide the study drug through DTP shipment in the event pandemic situation like COVID-19 or state of emergency prevent the study drug dispensation to the subject onsite, if permitted by local regulations.*

- Update Section 6.4, Adverse Events of Special Interest

Rationale: *Clarified and updated the list of the adverse events of special interest according to the revised sponsor guidelines.*

- Update Section 6.7, Adverse Event Collection Period

  Rationale: *Added supplemental COVID-19 case report forms (CRFs) for missed or virtual visits, study drug interruptions or discontinuations, or adverse events and instructions to collect safety information related to COVID-19.*

  Clarified that supplemental CRFs should be completed for renal and herpes zoster infection adverse events and for CPK increase considered by the Investigator to be an adverse event.

- Update Section 6.8, Serious Adverse Event Reporting

  Rationale: *Updated telephone number to contact the Immunology Safety Team for safety concerns and Therapeutic Area Medical Director contact information.*

- Update Section 6.9, Pregnancy

  Rationale: *Updated text to define Pregnancy reporting timeline as 24 hours from site staff awareness according to the sponsor requirements.*

- Update Section 6.10, Toxicity Management

  Rationale: *Added guidance for investigators on the management of subjects with suspected or confirmed COVID-19 infection during the study.*

- Update Table 5, Specific Toxicity Management Guidelines for Abnormal Laboratory Values

  Rationale: *Clarified that Investigator should contact the AbbVie TA MD for confirmed ALT or AST > 8 x ULN in addition to the immediate study drug interruption.*

- Added Section 6.12 Product Complaint

  Rationale: *Updated text to included product complaint definition and reporting expectations according to the sponsor requirements.*

- Update Section 7.0, Protocol Deviations

  Rationale: *Added language to include provision for modifications due to protocol deviations that may be due to pandemic like COVID-19 or state of*

emergency situations in order to guide investigators to notify IRB/EC when deviations occur. Updated contact information for current study team.

- Update Section 9.2, Ethical Conduct of the Study

  Rationale: *Inclusion of information regarding COVID-19 or any pandemic/state of emergency-related acceptable protocol modifications.*

- Update Section 9.3, Subject Information and Consent

  Rationale: *Added provision that in the event of a pandemic situation or state of emergency, verbal consent may be obtained in addition to the study informed consent in accordance with local regulations.*

- Update Section 10.1, Source Documents

  Rationale: *Noted that remote monitoring may be employed as needed, due to COVID-19 or any pandemic/state of emergency.*

- Update 15.0 Reference List

  Rationale: *Included the most recent Upadacitinib Investigator Brochure*

- Update Appendix A, Responsibilities of the Clinical Investigator

  Rationale: *Clarified that clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP).*

- Update Appendix B, List of Protocol Signatories

  Rationale: *Updated list of current Protocol Signatories*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-538
Name of Study Drug: Upadacitinib	**Phase of Development:** 2
Name of Active Ingredient: Upadacitinib	**Date of Protocol Synopsis:** 01 December 2020
Protocol Title: Phase 2 Study, Multicenter, Open-Label Extension (OLE) Study in Rheumatoid Arthritis Subjects who have Completed a Preceding Phase 2 Randomized Controlled Trial (RCT) with Upadacitinib (ABT-494)	
Objective: **Main Study** To evaluate the long-term safety, tolerability, and efficacy of upadacitinib RA subjects who have completed Study M13-550 or Study M13-537 Phase 2 RCT with upadacitinib. **Optional Vaccine Sub-study:** To assess the impact of upadacitinib treatment (15 mg QD or 30 mg QD) with a stable background of MTX on immunological responses following administration of Prevnar 13® pneumococcal vaccine in RA patients (Appendix O).	
Investigators: Multicenter	
Study Sites: 118 sites	
Study Population: Adult female and male RA subjects who have completed the Last Visit (Week 12) of Study M13-550 or Study M13-537 Phase 2 RCT with upadacitinib, and who have met all of the specified inclusion and exclusion criteria.	
Number of Subjects to be Enrolled: 494 subjects have been enrolled in this OLE study.	
Methodology: This is an extension study to assess the long-term safety, tolerability, and efficacy of upadacitinib in RA subjects who have completed Study M13-550 or Study M13-537 RCT with upadacitinib. Only those subjects who have met all of the specified inclusion and exclusion criteria will have an option to enter into the OLE study to receive upadacitinib, as long as the subject is willing and the Investigator believes that continuing the therapy with upadacitinib is appropriate. All eligible subjects will be assigned to upadacitinib 6 mg BID immediately after or up to 30 days following the Last Visit (Week 12) of Study M13-550 or Study M13-537. Subjects who are unable to tolerate 6 mg BID will be discontinued from the study. At Week 6, if a subject fails to achieve at least 20% improvement from RCT Baseline in **both** Tender Joint Count (TJC) and Swollen Joint Count (SJC), upadacitinib dose should be increased to 12 mg BID as long as the Investigator has no safety concerns. After 6 weeks of treatment with upadacitinib 12 mg BID, the improvement in TJC and SJC will be re-assessed at next scheduled visit (Week 12). If the subject on 12 mg BID fails to achieve at least 20% improvement in **both** TJC and SJC from RCT Baseline the subject will be discontinued. At Week 12, the same process will be followed. If a subject still on 6 mg BID fails to achieve at least 20% improvement from RCT Baseline in **both** TJC and SJC, upadacitinib dose should be increased to 12 mg BID. The improvement in TJC and SJC will be re-assessed after 6 weeks of treatment with 12 mg BID at Week 18 (an optional study visit). Subjects who fail to achieve at least 20% improvement from RCT Baseline in both TJC and SJC with 12 mg BID at Week 18 will be discontinued.	

Methodology (Continued):

After Week 12, if a subject fails to show at least 20% improvement from RCT Baseline in TJC and SJC at 2 consecutive scheduled study visits then the subject will be discontinued.

Starting at Week 6 and during any scheduled or unscheduled visits thereafter, upadacitinib dose may be increased from 6 mg BID to 12 mg BID (or 30 mg QD from January 2017, see below for more details) if a subject fails to achieve Low Disease Activity (LDA) status (CDAI > 10) and has no safety concerns per Investigator's judgment.

At any visit, upadacitinib dose may be decreased back to 6 mg BID (or 15 mg QD from January 2017) per Investigator's judgment if there are safety and/or tolerability concerns due to an adverse event or reaching one of the protocol specific toxicity management thresholds. Dose increase back to 12 mg BID (or 30 mg QD from January 2017) is not allowed.

From January 2017, all subjects who are at Week 72 or beyond will receive a once-daily tablet formulation. Subjects who are on 6 mg BID capsule dosing will be transitioned to 15 mg QD tablet dosing. Subjects who are on 12 mg BID capsule dosing will be transitioned to 30 mg QD tablet dosing. The capsule formulation will not be available to subjects once the transition to tablet formulation has occurred. Please see additional details in Section 5.1. Starting with Amendment 5, subjects who are receiving 30 mg QD open-label upadacitinib will have the option to decrease the dose to 15 mg QD based on investigator's discretion.

Prohibited Concomitant Medication

The following medications are prohibited throughout the study:

- All biologic therapies
- High potency opiates
- Live vaccines
- Anti-retroviral therapy
- Use of known strong CYP3A inhibitors (e.g., clarithromycin, conivaptan, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole, grapefruit (fruit or juice) or strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)
- Oral DMARDs (except MTX) are prohibited up to Week 24 but are allowed thereafter per Investigator's clinical judgment
- JAK inhibitors other than upadacitinib (including but not limited to tofacitinib [Xeljanz®], baricitinib and filgotinib)

Concomitant Therapy

- Subjects should continue with a stable prescription of methotrexate (MTX) treatment (7.5 to 25 mg/week) along with a stable dose of folic acid (or equivalent). If a subject experiences MTX-induced toxicity, MTX dose can be reduced or discontinued as per Investigator's medical judgment
- Stable doses of NSAIDs, acetaminophen
- PRN use of NSAIDs and acetaminophen is allowed, but should not be dosed during the 24 hours prior to a study visit
- Oral corticosteroids (equivalent to prednisone ≤ 10 mg but can be increased after Week 24)
- Intra-articular, intra-muscular, intra-bursa and intra-tendon sheath injections of corticosteroids

Methodology (Continued):

Study Drug Interruption

Subjects who, in the opinion of the investigator, develop adverse events that require study drug interruption and/or reach protocol specified toxicity management thresholds, can have the study drug interrupted for up to 30 days while recovering from the adverse event.

Pharmacokinetic Sample Collection

A single pharmacokinetic sample will be collected at study visits BL, Weeks 6, 12, 24, 36, 48, 72 and 96 without regard to the time of dosing. Blood samples for PK will be collected at any time during the visit, and preferably within 1 to 8 hours after the last dose. The exact date, time and number of capsules of the last 2 doses of study drug taken prior to the pharmacokinetic sample collection will be recorded to the nearest minute starting with the dose prior to PK collection.

Scheduled Study Visits

Study visits will occur at BL, Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 12 weeks thereafter until the end of the study, including a 30-day follow up (phone call or site) visit.

Optional Study Visit

At Week 18.

Duration

Approximately 312 weeks.

Study visits may be impacted by state of emergency or pandemic like COVID-19. If visits cannot be conducted onsite due to travel restrictions or other pandemic or state of emergency related reasons, virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others may be performed. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subjects who have completed Study M13-550 or Study M13-537 with upadacitinib and has not developed any discontinuation criteria, defined in Section 5.4.1 of that study.
2. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines while continuing study drug treatment. Prophylactic treatment must be completed.
3. If female, subject must be postmenopausal, OR permanently surgically sterile, OR for women of childbearing potential, practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 30 days after the last dose of study drug.
4. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of study drug, to practice the protocol-specified contraception (refer to Section 5.2.4).
5. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
6. Subject is judged to be in good health as determined by the Investigator based on the results of medical history, physical examination and laboratory profile performed.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued)

Main Exclusion:

1. Pregnant or breastfeeding female.
2. Ongoing infections at Week 0 that have NOT been successfully treated. Subjects with ongoing infections undergoing treatment may be enrolled BUT NOT dosed until the infection has been successfully treated.
3. Anticipated requirement or receipt of any live vaccine during study participation including up to 30 days after the last dose of study drug.
4. Laboratory values from the visit immediately prior to Baseline Visit* meeting the following criteria:
   - Serum aspartate transaminase (AST) or alanine transaminase (ALT) > 3.0 × ULN
   - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m^2
   - Total white blood cell count (WBC) < 2,000/µL
   - Absolute neutrophil count (ANC) < 1,000/µL
   - Platelet count < 50,000/µL
   - Absolute lymphocytes count < 500/µL
   - Hemoglobin < 8 gm/dL

   *Local requirements may apply. Refer to Appendix N for local requirements (United Kingdom).
5. Enrollment in another interventional clinical study while participating in this study.
6. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive study drug.

Investigational Product:	Upadacitinib 3 mg capsules, 12 mg capsules, 15 mg tablets, 30 mg tablets
Doses:	6 mg BID (initial dose assignment for all subjects). Upadacitinib doses of 6 mg BID, 12 mg BID, 15 mg QD and 30 mg QD are allowed during the OLE treatment period.
Mode of Administration:	Oral
Reference Therapy:	None (Open-Label Extension)
Duration of Treatment:	Approximately 312 weeks

Criteria for Evaluation:

Efficacy:

ACR20/50/70 response rates at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study will be evaluated based on 20/50/70% improvement in TJC, SJC, and ≥ 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Health Assessment Questionnaire Disability Index (HAQ-DI), and hsCRP.

Criteria for Evaluation (Continued):

Efficacy (Continued):

Change from Baseline in individual ACR components at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study will also be evaluated: TJC, SJC, Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Health Assessment Questionnaire Disability Index (HAQ-DI), and hsCRP. For analyses purposes, the baseline data for each subject will be the data collected immediately prior to starting double-blind-treatment.

The proportion of subjects achieving Low Disease Activity (LDA) or Clinical Remission (CR), and the proportion of subjects achieving CR will be evaluated at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study. The criteria will be based on DAS28 [CRP] or CDAI as follows:

	DAS28 [CRP]	CDAI
LDA	$2.6 \leq$ to < 3.2	$2.8 <$ to ≤ 10
CR	< 2.6	≤ 2.8

Change from Baseline in DAS28 [CRP] disease activity score, CDAI and Patient Reported Outcomes including FACIT-Fatigue Scale, RA-WIS, and EQ-5D will be analyzed at Weeks 6, 12, 24, 36, 48, 72, 96 and every 24 weeks thereafter until the end of the study.

Pharmacokinetic:

Individual plasma concentrations of upadacitinib will be tabulated and summarized.

Pharmacodynamic/Efficacy:

Changes from Baseline in in-vivo pharmacodynamic biomarkers and RA disease response biomarkers will be analyzed at Weeks 6, 12, 24 and 48.

Safety:

Safety evaluations will include adverse event monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology, chemistry, and urinalysis). Toxicity management guidelines are included in the protocol.

Statistical Methods:

Efficacy:

Baseline data for each subject will be the data collected at the visit immediately prior to starting double-blind treatment.

The response rates of ACR20/50/70 will be summarized with 95% confidence intervals by visit.

Change from Baseline will be summarized with descriptive statistics for TJC, SJC, Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, HAQ-DI, hsCRP, DAS28[CRP], CDAI, and Patient Reported Outcomes, including FACIT Fatigue Scale, RA-WIS and EQ-5D by visit.

Statistical Methods (Continued):

Efficacy (Continued):

The proportion of subjects achieving LDA (2.6 ≤ DAS28 [CRP] < 3.2 or 2.8 < CDAI ≤ 10) or CR (DAS28 [CRP] < 2.6 or CDAI ≤ 2.8), and the proportion of subjects achieving CR (DAS28 [CRP] < 2.6 or CDAI ≤ 2.8) will be summarized with 95% confidence intervals by visit.

In an alternate assessment for summarizing the response rates, baseline data will be assumed to be the data collected at the visit immediately prior to starting treatment with active upadacitinib.

Pharmacokinetic:

Individual plasma concentrations of upadacitinib will be tabulated and summarized. A mixed-effect modeling approach may be used to estimate the population central value and the empirical Bayesian estimates of the individual values for upadacitinib oral clearance (CL/F) and volume of distribution (V_{ss}/F). Additional parameters may be estimated if useful in the interpretation of the data.

Pharmacodynamic:

Changes from Baseline in in-vivo pharmacodynamic biomarkers and RA disease response biomarkers will be summarized with descriptive statistics by visit.

Safety:

All subjects who receive at least one dose of upadacitinib during the OLE period will be included in the safety analysis. Incidence of adverse events, serious adverse events, premature discontinuation, and changes from Baseline in vital signs, physical examination results and clinical laboratory values will be analyzed by visit. Treatment-emergent adverse events will be tabulated by system organ class and by MedDRA preferred term. Mean change from Baseline for laboratory and vital signs data will be summarized by visit. For analyses purposes, baseline for vital signs, physical examination results, and clinical laboratory results for subjects will be the data collected at the visit immediately prior to starting double-blind treatment.

In an alternate assessment for summarizing the safety and laboratory data, baseline data will be assumed to be the data collected at the visit immediately prior to starting treatment with active upadacitinib.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

α-CCP Ab	Anti-Cyclic Citrullinated Antibody
ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BP	Blood pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDAI	Clinical Disease Activity Index
CD4, CD8	Cluster Of Differentiation
CGC	Common Gamma-Chain
CHF	Congestive Heart Failure
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
COVID-19	Coronavirus Disease - 2019
CPK	Creatine Phosphokinase
CR	Clinical Remission
CRF	Case Report Form
CRP	C-Reactive Protein
CXR	Chest X-Ray
DAS	Disease Activity Score
DM	Diabetes Mellitus
DMARD	Disease-Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
DTP	Direct-to-Patient
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EDC	Electronic Data Capture
EQ-5D	EuroQoL-5D
EULAR	European League against Rheumatism
eGFR	Estimated glomerular filtration rate
ET	Early termination
FACIT	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GMCSF	Granulocyte macrophage colony-stimulating factor
gp130	Glycoprotein 130
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL	High Density Lipoprotein
hsCRP	High-Sensitivity C-Reactive Protein
HV	Healthy Volunteer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JAK	Janus Activated Kinase
LDA	Low Disease Activity
LDL	Low Density Lipoprotein
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NK	Natural Killer Cells
NKT	Natural Killer T Cells

NCS	Non-Clinically Significant
NOAEL	No Observable Adverse Effect Level
NRI	Non Responder Imputation
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OC	Observed Cases
OLE	Open-Label Extension
PE	Physical Examination
PG	Pharmacogenetic
PhGA	Physician's Global Assessment of Disease Activity on VAS
PK	Pharmacokinetic
PPD	Purified Protein Derivative
PtGA	Patient's Global Assessment of Disease Activity on VAS
QD	Once Daily
RA	Rheumatoid Arthritis
RAVE®	EDC System from Medidata
RBC	Red Blood Cell Count
RCT	Randomized Control Trial
RF	Rheumatoid Factor
RR	Respiratory Rate
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SGOT/AST	Serum Glutamic-Oxaloacetic Transaminase/Aspartate Transaminase
SGPT/ALT	Serum Glutamic-Pyruvic Transaminase/Alanine Transaminase
SJC	Swollen Joint Count
SOC	System Organ Class
STAT	Signal Transduction Activators of Transcription
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TJC	Tender Joint Count
T_{max}	Time to Maximum Observed Plasma Concentration
Tyk2	Tyrosine Kinase 2
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale

VTE	Venous Thromboembolic Events
WBC	White Blood cell Count
RA-WIS	Work Instability Scale – Rheumatoid Arthritis

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3.0 Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology. The hallmark feature of patients affected by RA is an inflammatory process manifested by persistent symmetric polyarthritis of synovial joints, and oftentimes includes systemic inflammatory manifestations in extra-articular organ systems. Early therapy with disease-modifying antirheumatic drugs (DMARDs) is the standard of care, although a significant proportion of patients either do not achieve disease remission or become refractory to available therapies as the disease progresses. Novel therapies are therefore required to complement the available interventions to address the unmet need in the treatment of patients with RA. Evidence suggests that inhibition of the Janus activated kinase (JAK)-mediated pathways is a promising approach for the treatment of patients with this chronic disorder.[1]

The JAK family is composed of 4 family members: JAK1, 2, 3, and Tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors such as common gamma-chain (CGC) receptors and the glycoprotein 130 (gp130) transmembrane proteins.[2] Almost 40 cytokine receptors signal through combinations of these four JAKs and their seven downstream substrates of the Signal Transduction Activators of Transcription (STAT) family.[3] Activation of these JAK-related pathways initiates expression of survival factors, cytokines, chemokines and other molecules that facilitate leukocyte cellular trafficking and cell proliferation which contribute to inflammatory and autoimmune disorders.

JAK3 and JAK1 are components of the CGC cytokine receptor complexes and blockade of either inhibits signaling by the inflammatory cytokines interleukin (IL)-2, 4, 7, 9, 15 and 21.[3] Furthermore, other pathologically relevant cytokines such as IL-6 are known to recruit JAK1, JAK2 and Tyk2 upon binding to its receptor, with IL-6 appearing to signal predominantly via JAK1.[4,5] Hence, the JAK family has evoked considerable interest in the area of inflammatory diseases leading for the development of various JAK inhibitors with different selectivity profiles against JAK1, JAK2, JAK3 and Tyk2. Tofacitinib (Xeljanz®; Pfizer®) is a non-selective JAK inhibitor that targets all 4 members of the JAK

family; the rank order of cellular potency is JAK3, JAK1, JAK2 and Tyk2.[1] Tofacitinib is approved in the United States and is indicated for treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX.[9] The approved dose is 5 mg BID and it can be used as monotherapy or in combination with MTX or other non-biologic disease-modifying antirheumatic drugs (DMARDs). Recently tofacitinib was approved in Japan, Russia, and Switzerland.

Upadacitinib is a novel JAK1 inhibitor being developed for the treatment of adult patients with moderately to severely active RA, either alone or in combination with methotrexate (MTX) or other non-biologic DMARDs. Based on in vitro selectivity assays and in-vivo animal models, upadacitinib has demonstrated that inhibiting JAK1 with minimal impact on JAK2 is feasible at efficacious drug exposure levels. Thus, the enhanced selectivity of upadacitinib has the potential for an improved benefit/risk profile in treating patients with RA by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis. Also, the minimum of activity of upadacitinib against JAK3, which is involved in IL-15 signal transduction cascade, could potentially minimize a decrease in NK cell counts observed with tofacitinib clinical development program that may have contributed to increased incidences of viral infection, re-activation of herpes zoster, and malignancies.

The toxicology profile of upadacitinib has been evaluated in multiple chronic studies in rats and dogs. Briefly, nonadverse findings in rats included mild decreases in red blood cell counts, hemoglobin and dose-dependent decreases in circulating lymphocytes. At very high doses of upadacitinib (50 to 100 mg/kg/day) the adverse findings included mortality as well as tubular degeneration/regeneration in the kidney and liver necrosis. In dog studies there were dose-related decreases in hemoglobin and red cell mass (red blood cell counts, hemoglobin concentration, hematocrit) and microscopic findings in popliteal lymph nodes (mixed cell inflammation in inter-digital skin of paws and draining lymph nodes) considered secondary to potential upadacitinib-related immunomodulation. A detailed summary of the pre-clinical toxicology results can be found in the current Investigator's Brochure.[6]

There have been two clinical studies of upadacitinib. The clinical conduct of Study M13-401, a single-dose ascending dose study of upadacitinib at 1 mg up to 48 mg, has been completed. This study also included an assessment of the effect of food on the pharmacokinetics of upadacitinib. Preliminary results indicated that food had no effect on the exposure (AUC) of upadacitinib. Therefore, upadacitinib can be administered with or without food in the present study.

Preliminary results after multiple ascending doses of upadacitinib in healthy volunteers are available from Study M13-845. The randomized, double-blind, placebo controlled study was designed to evaluate the safety, tolerability and PK of upadacitinib at four dose levels of 3 mg, 6 mg, 12 mg and 24 mg BID. In each dose group, 8 subjects were randomly assigned to receive upadacitinib and 3 subjects received placebo administered twice daily (BID) for 14 consecutive days. No serious or fatal adverse events or AEs leading to discontinuation were reported during the study. Treatment-emergent adverse events (TEAE) were reported in 7 (58.3%) subjects receiving placebo and in 11 (34.3%) subjects receiving ABT-494 with the overall incidence of TEAEs at 2 (25.0%), 2 (25.0%), 3 (37.5%) and 4 (50%) of subjects experienced TEAEs in the 3 mg, 6 mg, 12 mg and 24 mg dose groups, respectively. All TEAEs were considered mild (Grade 1) in severity and reported to have a reasonable possibility of being related to study drug except 2 events in one subject in the placebo group were considered as having no reasonable possibility of being related. The most common TEAEs in the upadacitinib treatment groups (n = 32) were headache (15.6%), abdominal pain (6.3%), diarrhea (6.3%), and nasopharyngitis (6.3%). No clinically meaningful changes in laboratory values, vital signs or ECG findings were observed during the study.

Preliminary results indicated that at steady state, upadacitinib had minimal to no accumulation with a median T_{max} of approximately 2 hours and an effective half-life of approximately 3 hours. Upadacitinib exposure was approximately dose-proportional across the dose range studied. Approximately 19% to 21% of upadacitinib was excreted as unchanged parent in the urine during a dose interval in the steady state.

A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with upadacitinib can be found in the current Investigator's Brochure.[6]

3.1 Differences Statement

This OLE study is designed to collect long-term safety, tolerability, and efficacy data. Collecting long-term safety data is important to assess the risk to benefit profile of upadacitinib. All subjects who have completed the Last Visit (Week 12) of Study M13-550 or Study M13-537 upadacitinib Phase 2 RCT (12 – 24 weeks) will have an opportunity to enroll into this OLE study. This is the first study with upadacitinib of treatment durations longer than 24 weeks.

3.2 Benefits and Risks

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease characterized by inflammation of the articular synovial membrane. If left untreated, RA causes damage to cartilage, bone, and adjoining tissues which ultimately leads to severe disability, impaired function, and marked reduction in the quality of life of subjects. The prevalence of RA in the general population is approximately 1%, and increases with age in both genders, with women being more prone for developing RA than men.

The etiology of RA has not been fully elucidated, but based on the pathologic mechanisms of RA, several pro-inflammatory pathways and cytokines such as TNF, interferon gamma, IL-1 and other interleukins have been identified in promoting synovial inflammation and bone and cartilage destruction. Clinical efficacy in targeting these proinflammatory cytokines and downstream signaling pathways has been well validated in RA. Several inhibitors of Janus activated kinases (JAKs), a family of intracellular tyrosine kinases that transduces cytokine-mediated signals, demonstrated proof of concept first with currently marketed tofacitinib and with other emerging second generation JAK inhibitors that are in the clinic for reducing the signs and symptoms in RA subjects.[11,12]

The JAK family of tyrosine kinases comprises 4 members, JAK1, JAK2, JAK3 and TYK2. The second generation of JAK inhibitors currently in development for RA

displays a varying potency and selectivity directed at members of the JAK family.[1] Tofacitinib is a non-selective JAK inhibitor targeting JAK1, JAK2 and JAK3, but most potently inhibits JAK3.[1] Although tofacitinib improves the clinical signs and symptoms of RA, questions remain surrounding the safety profile regarding the incidences of serious infection, malignancies, herpes zoster, and hematologic adverse events.

Data from clinical studies in RA subjects with tofacitinib showed reduced levels of hemoglobin, absolute lymphocytes counts, and total white blood cell counts in some subjects and also increased serum creatinine; total cholesterol, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C); and liver transaminases (ALT and AST).[7,8] The increases in serum creatinine, lipids, and liver transaminase values typically have been asymptomatic, reversible, and were not associated with any overt declines in renal or hepatic function.

Upadacitinib is a novel JAK1 selective inhibitor with minimal inhibitory effects on JAK2 and JAK3, which could potentially minimize some of the reported safety concerns with non-selective JAK inhibitors which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways. Initiation of Phase 2 studies with upadacitinib was feasible based on acceptable safety and tolerability profile of upadacitinib in single ascending dose and multiple ascending dose studies in healthy volunteers. The current OLE study will allow the collection of long-term safety data to better assess the risk to benefit profile of upadacitinib.

In view of the COVID-19 pandemic, the benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

4.0 Study Objective

The primary objective is to evaluate the long-term safety, tolerability, and efficacy of upadacitinib in RA subjects who have completed Study M13-550 or Study M13-537 Phase 2 RCT with upadacitinib.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 2, multicenter, OLE study to assess the long-term safety, tolerability, and efficacy of upadacitinib in RA subjects who have completed Study M13-550 or Study M13-537 Phase 2 RCT with upadacitinib. This study is designed to enroll up to 500 subjects. Subjects will be treated for approximately 312 weeks.

Only those subjects who have met all of the specified inclusion criteria and none of the exclusion criteria will have an option to enter into the OLE study to receive upadacitinib, as long as the subject is willing and the Investigator believes that continuing therapy with upadacitinib is appropriate.

All eligible subjects will be assigned to upadacitinib 6 mg BID immediately after or up to 30 days following the Last Visit (Week 12) of Study M13-550 or Study M13-537 Phase 2 RCT.

Subjects who are unable to tolerate 6 mg BID will be discontinued from the study.

At Week 6, if a subject fails to achieve at least 20% improvement from RCT Baseline in both Tender Joint Count (TJC) and Swollen Joint Count (SJC), upadacitinib dose should be increased to 12 mg BID as long as the Investigator has no safety concerns. After 6 weeks of treatment with upadacitinib 12 mg BID, the improvement in TJC and SJC will be re-assessed at next scheduled visit (Week 12).

If the subject on 12 mg BID fails to achieve at least 20% improvement in both TJC and SJC from RCT Baseline the subject will be discontinued.

At Week 12, the same process will be followed. If a subject still on 6 mg BID fails to achieve at least 20% improvement from RCT Baseline in both TJC and SJC, upadacitinib dose should be increased to 12 mg BID. The improvement in both TJC and SJC will be re-assessed after 6 weeks of treatment with 12 mg BID at Week 18 (an optional study visit).

Subjects who fail to achieve at least 20% improvement from RCT Baseline in both TJC and SJC with 12 mg BID at Week 18 will be discontinued.

After Week 12, if a subject fails to show at least 20% improvement from RCT Baseline in both TJC and SJC at 2 consecutive scheduled study visits, the subject will be discontinued.

Starting at Week 6 and during any scheduled or unscheduled visits thereafter, upadacitinib dose may be increased from 6 mg BID to 12 mg BID (or 30 mg QD from January 2017, see below) if a subject fails to achieve Low Disease Activity (LDA) status (defined by CDAI > 10) and has no safety concerns per Investigator's judgment.

At any visit, upadacitinib dose may be decreased back to 6 mg BID (or 15 mg QD from January 2017) per Investigator's judgment if there are safety and/or tolerability concerns, due to an adverse event or reaching one of the protocol specific toxicity management thresholds. Dose increase back to 12 mg BID (or 30 mg QD from January 2017) is not allowed.

From January 2017, all subjects who are at Week 72 or beyond will receive a once-daily tablet formulation. Subjects who are on 6 mg BID capsule dosing will be transitioned to 15 mg QD tablet dosing. Subjects who are on 12 mg BID capsule dosing will be transitioned to 30 mg QD tablet dosing. The capsule formulation will not be available to subjects once the transition to tablet formulation has occurred.

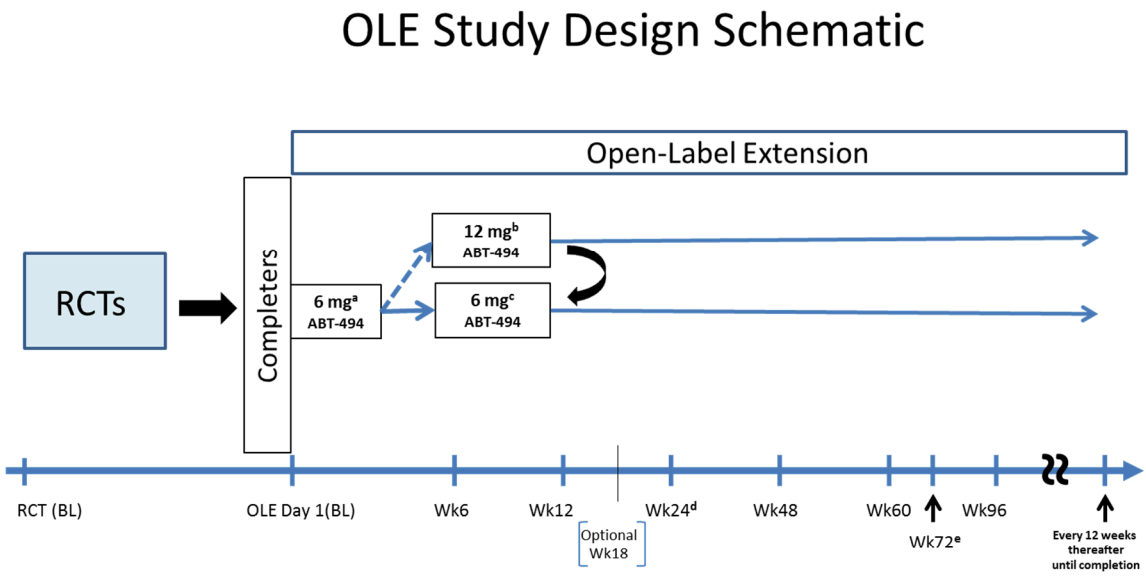
Starting with Amendment 5, subjects who are receiving 30 mg QD open-label upadacitinib will have the option to decrease the dose to 15 mg QD based on investigator's discretion.

The change to once daily tablet formulation in this study is based on extrapolation of pre-clinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the Phase 1 studies in healthy volunteers (single and multiple ascending dose Studies M13-401 and M13-845, respectively) and completed Phase 2b randomized, controlled studies (RCTs) in RA subjects (Studies M13-537 and M13-550). The doses

selected, 15 mg QD and 30 mg QD, are expected to approximate the exposures achieved with the 6 mg BID and 12 BID immediate release formulations, respectively, which should be efficacious with an acceptable safety profile. Preliminary results from an ongoing relative bioavailability study demonstrated that single 15 mg and 30 mg doses of the once-daily formulation provide comparable AUC and significantly lower C_{max} than single doses of 12 mg immediate release (IR) formulation (AUC equivalent to 6 mg BID dose tested in Phase 2) and 24 mg IR formulation (AUC equivalent to 12 mg BID dose tested in Phase 2), respectively, under fasting conditions. At steady-state, the once-daily dose of 15 mg QD is predicted to achieve comparable daily AUC and C_{max}, and non-inferior C_{trough} to 6 mg BID IR formulation. In the Phase 2 RCTs, the 6 mg BID dose was shown to achieve the near maximum efficacy. The once-daily dose of 30 mg QD is predicted to achieve comparable daily AUC and C_{max}, and non-inferior C_{trough} to 12 mg BID IR formulation. In the Phase 2 RCTs, the 12 mg BID dose was clearly shown to achieve the plateau of efficacy.

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

Figure 1. Study Design Schematic



[a] On day 1 all eligible subjects will be assigned to ABT-494 6 mg BID immediately after or up to 30 days following the Last Visit (Week 12) of M13-550 or M13-537.
[b] At Weeks 6 and 12, if a subject fails to achieve a 20 % improvement in **both** TJC and SJC, ABT-494 dose should be up-titrated from 6 mg BID to 12 mg BID, and Investigator should re-assess TJC and SJC improvement after an additional 6 weeks of treatment with 12 mg BID. In addition, during any scheduled or unscheduled study visits, ABT-494 dose can be increased to 12 mg BID if a subject fails to achieve Low Disease Activity Status (defined as CDAI > 10).
[c] At any visit, ABT-494 dose may be decreased back to 6 mg BID per Investigator's judgment **only** due to adverse events or reaching one of the protocol specific toxicity management thresholds. Dose increase back to 12 mg BID is not allowed.
[d] After 24 weeks of treatment with open-label ABT-494, initiation of or change in a subject's concomitant medications for RA, including MTX and other csDMARDs or corticosteroids (oral or parenteral) is allowed.
[e] From January 2017, all subjects at Week 72 or beyond will receive a QD tablet formulation. Subjects on 6 mg BID will be transitioned to 15 mg QD dosing. Subjects on 12 mg BID will be transitioned to 30 mg QD dosing.

Prevnar 13® Sub-study

This optional sub-study of Study M13-538 will assess the impact of upadacitinib treatment (15 mg QD or 30 mg QD) with a stable background of MTX on immunological responses following administration of Prevnar 13® pneumococcal vaccine in RA patients. Methods, procedures and statistical analyses pertaining to this sub-study are provided in Appendix O.

Treatment Period

The treatment period for OLE can begin immediately after or up to 30 days following the Last Visit (Week 12) of Study M13-550 or Study M13-537 RCT and will continue for approximately 312 weeks in OLE. At Last Visit (Week 12) or up to 30 days following the Last Visit (Week 12) of Study M13-550 or Study M13-537, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the study. Subjects will visit the study site at Weeks 6, 12, 18 (Optional), 24, 36, 48, 60, 72, 84, 96 and every 12 weeks thereafter until the end of the study or if they terminate early from the study. A ± 7-day window is permitted around scheduled study visits. The last dose of study drug is taken the evening prior to the final visit.

Subjects may discontinue study drug treatment at any time during study participation. Subjects that end study participation early will have a Premature Discontinuation Visit and complete the procedures outlined for Premature Discontinuation Visit in Table 2 as soon as possible, preferably within 2 weeks of study drug discontinuation and preferably prior to initiation of another therapy.

Starting with Amendment 5, subjects who are receiving 30 mg QD open-label upadacitinib will have the option to decrease to the 15 mg QD dose based on investigator's discretion.

Follow-Up Period

All subjects will have a follow-up visit approximately 30 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs), and to collect vital signs and clinical laboratory tests. The 30 day follow up visit may be a telephone call if a site visit is not possible. Vital signs and laboratory test may not be required.

Protocol Modifications due to State of Emergency or Pandemic like COVID-19

Study visits may be impacted by a pandemic situation (including the COVID-19 pandemic) or any state of emergency. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others may be performed. Additional details are provided in the subsequent sections. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

5.2 Selection of Study Population

It is anticipated that up to 500 subjects, who have completed Study M13-550 or Study M13-537 RCT with upadacitinib, will enroll in this OLE study.

Only those subjects who have met all of the specified inclusion and none of the exclusion criteria in Section 5.2.1 and Section 5.2.2 will have an option to enter into the OLE study to receive upadacitinib, as long as the subject is willing and the Investigator believes that continuing the therapy with upadacitinib is appropriate.

5.2.1 Inclusion Criteria

1. Subjects who have completed preceding RCT study with upadacitinib and have not developed any discontinuation criteria, defined in Section 5.4.1 of that study.
2. Subject with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines while continuing study drug treatment. Prophylactic treatment must be completed.
3. If female, subject must be postmenopausal, OR permanently surgically sterile, OR for women of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 30 days after the last dose of study drug.

4. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of study drug, to practice the protocol-specified contraception (refer to Section 5.2.4).
5. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
6. Subject is judged to be in good health as determined by the Investigator based on the results of medical history, physical examination and laboratory profile performed.

Criteria	Rationale
1 – 2	To select the appropriate subject population.
3 – 4	The effect of upadacitinib on pregnancy and reproduction is unknown.
5 – 6	In accordance with harmonized Good Clinical Practice (GCP).

5.2.2 Exclusion Criteria

1. Pregnant or breastfeeding female.
2. Ongoing infections at Week 0 that have NOT been successfully treated. Subjects with ongoing infections undergoing treatment may be enrolled BUT NOT dosed until the infection has been successfully treated.
3. Anticipated requirement or receipt of any live vaccine during study participation including up to 30 days after the last dose of study drug.
4. Laboratory values from the visit immediately prior to Baseline Visit* meeting the following criteria:
   - Serum aspartate transaminase (AST) or alanine transaminase (ALT) > 3.0 × ULN
   - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m^2

- Total white blood cell count (WBC) < 2,000/µL
- Absolute neutrophil count (ANC) < 1,000/µL
- Platelet count < 50,000/µL
- Absolute lymphocytes count < 500/µL
- Hemoglobin < 8 gm/dL

*Local requirements may apply. Refer to Appendix N for local requirements (United Kingdom).

5. Enrollment in another interventional clinical study while participating in this study.
6. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive study drug.

Criteria	Rationale
1	The impact of upadacitinib on pregnancy and nursing is unknown
2 – 6	To ensure safety of the subjects throughout the study

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements including folic acid) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate eCRF.

Subjects should remain on a stable dose of MTX throughout the first 24 weeks of Study M13-538. However, if a subject experiences MTX-induced toxicity, MTX dose can be reduced or discontinued as per Investigator's medical judgment.

After 24 weeks of treatment with open-label upadacitinib, initiation of or change in a subject's concomitant medications for RA, including MTX and other csDMARDs or corticosteroids (oral or parenteral) is allowed.

Stable doses of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or oral corticosteroids (equivalent to prednisone ≤ 10 mg) are allowed throughout the study. PRN use of NSAIDs, acetaminophen, tramadol, codeine, propoxyphene and hydrocodone is allowed except 24 hours prior to any study visit.

Intra-articular, intra-muscular, intra-bursa and intra-tendon sheath injections of corticosteroids, dosage and frequency per standard of care, are allowed during the study. Details of each injection, along with the name of the joint injected, must be captured on appropriate eCRF as mentioned above. Subjects should have their joint(s) scored prior to receiving the injection. Any injected joints will be scored as **"NA = no assessment"** for 90 days from the time of injection.

The AbbVie Therapeutic Area Medical Director identified in Section 6.8 (Adverse Event Reporting) should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prohibited Therapy

The following medications are prohibited throughout the study:

- All biologic therapies
- JAK inhibitors other than upadacitinib (including but not limited to tofacitinib, baricitinib and filgotinib)
- High potency opiates
- Live vaccines
    - If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) 4 weeks before first dose of study drug with appropriate precautions or administered at least 30 days after last dose of study drug.
- Anti-retroviral therapy
- Use of known strong CYP3A inhibitors or strong CYP3A inducers. The most common strong CYP3A inhibitors and inducers are listed in Table 1.

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

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

- Oral DMARDs (except MTX) are prohibited up to Week 24 but are allowed thereafter per Investigator's clinical judgment. The following csDMARDs are allowed: MTX, sulfasalazine, hydroxychloroquine, chloroquine, and leflunomide. A combination of up to two background csDMARDs is allowed except the combination of MTX and leflunomide

5.2.4 Contraception Recommendations

Contraception Recommendation for Females

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

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

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

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

If, during the course of the study, a woman becomes surgically sterile or post-menopausal and complete documentation is available, contraception measures as defined above are no longer required.

Contraception Recommendation for Males

There are no contraception requirements for male subjects or their female partner(s).

It is important to note that subjects taking concomitant csDMARDs (i.e., methotrexate, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide) the duration of contraception and requirement not to donate sperm after discontinuation of these prescribed csDMARDs should be based on the local label.

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures will be performed as summarized in Table 2. All subjects must meet the study selection criteria outlined in Section 5.2.1 and Section 5.2.2 in order to be eligible for the study.

Study visits may be impacted by state of emergency or pandemic situations like COVID-19. This may include changes such as virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in Section 5.3.1.1. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.

Supplemental study case report forms should be completed in the event of missed/virtual visits, or study drug interruptions or discontinuations related to COVID-19.

Study Visits and/or activities should be performed as scheduled whenever possible. During a state of emergency or pandemic situation, if it is not possible for all study

procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, study visits may be conducted in a subject's home residence (see Section 5.3.1.1 – Sub-Section "Optional Home Healthcare Service Due to State of Emergency or Pandemic Situation like COVID-19").
- The following study activities may be performed virtually by phone/video conference:
  - Adverse event assessment
  - Concomitant therapy assessment including compliance to contraception requirements, if applicable
  - Latent TB risk assessment
  - Communication of in-home urine pregnancy test result
  - Dispense study drug and subject dosing diary (see Section 5.3.1.1 - Sub-Section "Study Drug Dispensing, Dosing, and Compliance" for details about the Direct-to-Patient shipment)
  - Review of subject dosing diary, compliance to IP administrations
- During a virtual visit, the following activities should not be performed:
  - Patient Questionnaires including Patient's Global Assessment of Disease Activity and Patient's Assessment of Pain
  - Vital Signs and Body Weight
  - Physical Examination
  - Physician's Global Disease Activity VAS (PhGA)
  - Tender Joint Count (TJC) 68/Swollen Joint Count (SJC)66
- The following study activities may be performed by a local clinic/ hospital/ laboratory:
  - QuantiFERON-TB Gold test or equivalent (and/or local PPD skin test)
  - Chest X-Ray, if the Investigator has determined, based on clinical judgement, that a CXR is required to ensure that it is safe to continue study

drug administration (e.g., subjects with seroconversion on an annual TB test).

In this case, CXR should be performed as soon as restrictions allow at the study site or local hospital/facility. Otherwise, the CXR will be performed at the next earliest feasible visit.

- 12-lead ECG, if the Investigator has determined, based on clinical judgement, that an ECG is required to ensure that it is safe to continue study drug administration In this case, ECG should be performed as soon as restrictions allow at the study site or local hospital/facility. Otherwise, the ECG will be performed at the next earliest feasible visit.
- Local urine pregnancy test
- Lab tests (blood chemistry, hematology, urinalysis)

All procedures performed at local facilities must be performed by appropriately qualified personnel.

- Lab draws should be obtained as close as possible to the scheduled visit.
- The study site should keep records of all visits/study activities performed virtually by phone/video or through the optional Home Healthcare Service or by a local clinic/hospital/laboratory.

Table 2. Study Activities

Activity	BL/Wk 0[a]	Wk 6	Wk 12	Wk 18 (Optional)[b]	Wk 24	Wk 36	Unscheduled Visit[c]	Premature Discontinuation	30-Day Follow-Up Visit[q]
Informed Consent[d]	X								
Patient's Global Assessment of Disease Activity (PtGA)[e]	X	X	X		X	X		X	
Patient's Assessment of Pain (VAS)[e]	X	X	X		X	X		X	
HAQ-DI[e]	X	X	X		X	X		X	
Work Instability Scale for RA (RA-WIS)[e]	X	X	X		X	X		X	
FACIT[e]	X	X	X		X	X		X	
EuroQol-5D (EQ-5D)[e]	X	X	X		X	X		X	
Medical/Surgical History[f]	X								
Vital Signs[g]	X	X	X		X	X	X	X	X
Body Weight	X	X	X		X	X	X	X	X
Physical Examination[h]	X								
Physician's Global Disease Activity VAS (PhGA)	X	X	X		X	X		X	
Tender Joint Count (TJC)68	X	X	X	X	X	X	X	X	X
Swollen Joint Count (SJC)66	X	X	X	X	X	X	X	X	X
Concomitant Therapy[i]	X	X	X	X	X	X	X	X	X
Adverse Event Assessment[j]	X	X	X	X	X	X	X	X	X
Pregnancy Test[k]	X	X	X		X	X	X	X	X

Table 2. Study Activities (Continued)

Activity	BL/Wk 0[a]	Wk 6	Wk 12	Wk 18 (Optional)[b]	Wk 24	Wk 36	Unscheduled Visit[c]	Premature Discontinuation	30-Day Follow-Up Visit[q]
Blood Chemistry[l]	X	X	X		X	X	X	X	X
Hematology (CBC)[l]	X	X	X		X	X	X	X	X
Urinalysis	X	X	X		X	X	X	X	X
hsCRP[l]	X	X	X		X	X		X	X
Disease Response Biomarker	X	X	X		X				
In-vivo Pharmacodynamic Biomarker Sample	X	X	X		X				
Blood Sample for upadacitinib PK Assay[m]	X	X	X		X	X		X	
Latent TB Risk Factor Questionnaire[n]						X			
PPD Skin Test or Quanti-FERON-TB Gold Test[n]						X			
Chest X-Ray[n]						X	X		
12-Lead ECG[o]							X		
Enrollment	X								
Dispense Study Drug	X	X	X	X	X	X	X		
Dispense Dosing Diary	X	X	X	X	X	X			
Review and Copy Subject Dosing Diary and Returned Used/Unused Study Drug	X	X	X	X	X	X	X	X	

Table 2. Study Activities (Continued)

Activity	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	Every 12 Weeks Until Study Completion	Every 48 Weeks Until Study Completion (Wk 132, Wk 180 Wk 228 and Wk 276)	Final Visit	Unscheduled Visit[c]	Premature Discontinuation	30-Day Follow-Up Visit[q]
Patient's Global Assessment of Disease Activity (PtGA)[e]	X	X	X	X	X	X		X		X	
Patient's Assessment of Pain (VAS)[e]	X	X	X	X	X	X		X		X	
HAQ-DI[e]	X	X	X	X	X	X		X		X	
Work Instability Scale for RA (RA-WIS)[e]	X		X		X	X		X		X	
FACIT [e]	X		X		X	X		X		X	
EuroQol-5D (EQ-5D)[e]	X		X		X	X		X		X	
Vital Signs[g]	X	X	X	X	X	X		X	X	X	X
Body Weight	X	X	X	X	X	X		X	X	X	X
Physical Examination[h]	X				X		X	X			
Physician's Global Disease Activity VAS (PhGA)	X	X	X	X	X	X		X		X	
Tender Joint Count (TJC)68	X	X	X	X	X	X		X	X	X	X
Swollen Joint Count (SJC)66	X	X	X	X	X	X		X	X	X	X
Concomitant Therapy[i]	X	X	X	X	X	X		X	X	X	X
Adverse Event Assessment[j]	X	X	X	X	X	X		X	X	X	X
Pregnancy Test[k]	X	X	X	X	X	X		X	X	X	X
Blood Chemistry[l]	X	X	X	X	X	X		X	X	X	X

Table 2. Study Activities (Continued)

Activity	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	Every 12 Weeks Until Study Completion	Every 48 Weeks Until Study Completion (Wk 132, Wk 180 Wk 228 and Wk 276)	Final Visit	Unscheduled Visit[c]	Premature Discontinuation	30-Day Follow-Up Visit[q]
Hematology (CBC)[l]	X	X	X	X	X	X		X	X	X	X
Urinalysis	X	X	X	X	X	X		X	X	X	X
hsCRP[l]	X	X	X	X	X	X		X		X	X
Disease Response Biomarker	X										
In-vivo Pharmacodynamic Biomarker Sample	X										
Blood Sample for upadacitinib PK Assay[m]	X		X		X					X	
Latent TB Risk Factor Questionnaire[n]				X			X				
PPD Skin Test or Quanti-FERON-TB Gold Test[n]				X			X				
Chest X-Ray[n]				X			X		X		
12-Lead ECG[o]	X				X		X		X		
Dispense Study Drug[p]	X	X	X	X	X	X			X		
Dispense Dosing Diary	X	X	X	X	X	X					
Review and Copy Subject Dosing Diary and Returned Used/Unused Study Drug	X	X	X	X	X	X		X	X	X	

BL = Baseline; Wk = Week

Table 2. Study Activities (Continued)

a. These procedures are completed at the Last Visit (Week 12) of preceding RCTs and results will serve as Baseline/Week 0 (Day 1) Visit results for Study M13-538. This applies to patients who enroll into OLE within 14 days following the last visit in RCTs. For subjects who enroll after 14 days following Week 12 of preceding RCTs, all procedures for Baseline (Week 0) visit will need to be repeated.

b. Subjects who do not achieve 20% improvement from Baseline (RCT period) in TJC and SJC, and their study drug dose is increased to 12 mg BID at Week 12, will have to return to clinic at Week 18 in order to accommodate TJC and SJC assessment after 6 weeks of treatment with 12 mg BID. Subjects who fail to achieve at least 20% improvement from Baseline (RCT period) in TJC and SJC with 12 mg BID at Week 18 in OLE will be discontinued.

c. Unscheduled Visit study activities should only be done as clinically indicated per Investigator's judgment.

d. Obtain prior to performing/collecting any study related procedures.

e. Prior to any procedures performed at all clinic visits.

f. Update Medical/Surgical History.

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

h. A complete physical examination will be done at Weeks 0, 48, 96 and every 48 weeks until end of the study and at the Final Visit. A symptom-directed physical exam will be performed when necessary, as per Investigator's judgment.

i. Concomitant Medication ending prior to first dose in Study M13-538 will be recorded in preceding RCT trials. Ongoing medications from preceding RCT trials after first dose in Study M13-538 will be recorded in Study M13-538.

j. Adverse Events ending prior to first dose in Study M13-538 will be recorded in preceding RCT trials. Ongoing Adverse Events from preceding RCT trials after first dose in Study M13-538 will be recorded in Study M13-538.

k. For women of childbearing potential, urine pregnancy test will be performed monthly at home between scheduled study visits. The results of these tests will be verbally communicated (via telephone) to the site. If a urine pregnancy test is positive, the subject must stop dosing, come in to clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory. A urine pregnancy test will be performed at all scheduled study visits as specified in Table 2, on all female subjects of childbearing potential. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive at any visit, withhold dosing and perform a serum pregnancy test for confirmation. The serum pregnancy test will be sent to and performed by the central laboratory. Pregnant subjects must be discontinued from the study. In the event a pregnancy test comes back borderline or indeterminate, a repeat test is required.

l. Fasting status for each subject should be documented in the source documents. Fasting is NOT required for this study.

m. Blood samples for PK will be collected at any time during the visit, and preferably within 1 to 8 hours after the last dose. The exact date, time and number of capsules of the last 2 doses of study drug taken prior to the pharmacokinetic sample collection will be recorded to the nearest minute starting with the dose prior to PK collection.

Table 2. Study Activities (Continued)

n. TB testing should be performed every 48 weeks after Week 84 in subjects with previous negative QuantiFERON-TB Gold and/or PPD tests. Subjects with documentation of a prior positive result of QuantiFERON-TB Gold and/or PPD tests are not required to repeat either test during the study and should be considered positive. Subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines. Refer to Section 5.3.1.1 TB Testing/TB Prophylaxis for additional details. Study drug(s) should not be withheld at the time of the first positive TB test. Obtain chest x-ray for subjects with new TB risk factors as identified by the TB risk factor questionnaire or for subjects living in areas endemic for TB or for subjects with newly positive PPD or QuantiFERON-TB Gold at Week 36, Week 84, and every 48 weeks (Wk 132, Wk 180, Wk 228 and Wk 276) until the end of the study or as clinically indicated during the study.

o. 12-Lead ECG will only be done for those subjects who did not have ECG done at their Last Visit (Week 12) in Study M13-550 or Study M13-537 or if it is required in the opinion of the Investigator. ECG should be done for all subjects at Weeks 0, 48, 96 and every 48 weeks after Wk 84 (Wk 132, Wk 180, Wk 228 and Wk 276) until the end of the study or as clinically indicated during the study.

p. From January 2017, all subjects who are at Week 72 or beyond will receive once-daily tablet formulation. Subjects who are on 6 mg BID dosing will be transitioned to 15 mg QD dosing. Subjects who are on 12 mg BID dosing will be transitioned to 30 mg QD dosing. The capsule formulation will not be available to subjects once the transition to tablet formulation has occurred.

q. The 30-day follow up visit may be a telephone call if a site visit is not possible. Vital signs and laboratory test may not be required.

5.3.1.1 Study Procedures

Study procedures will be performed during study visits as specified in Table 2. The study procedures outlined in Table 2 are discussed in detail in this section, with the exception of drug concentration measurements (discussed in Section 5.3.2), disease response biomarkers (Section 5.3.1.3), and the collection of Concomitant Medication (discussed in Section 5.2.3) and adverse event (AE) information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

Subjects will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved, informed consent form before any study procedures are performed on the subject in order to participate in this study. Details regarding how informed consent will be obtained and documented are provided in Section 9.3. Written consent will be required for a subject in order to participate in the optional vaccine sub-study (Appendix O).

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at the Baseline/Week 0 visit.

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

At visits specified in Table 2, the subject will rate the severity of the RA symptoms within the last 24 hours and how he/she is doing from 0 to 100 using the Visual Analog Scale, which consists of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed. This assessment will be used for the DAS28 [CRP] calculation in this study (Appendix E).

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, the Patient's Global

Assessment of Disease Activity will be completed by the physician at the next feasible visit.

Patient's Assessment of Pain Visual Analog Scale (VAS)

At visits specified in Table 2, the subject will rate the severity of pain due to rheumatoid arthritis in the past week from 0 to 100 (Appendix F) using the Visual Analog Scale, which consists of a horizontal 100 mm line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed.

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

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, the Patient's Assessment of Pain will be completed by the physician at the next feasible visit.

Health Outcomes Questionnaires

Subjects will complete the following questionnaires as specified in Table 2:

- Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess the physical function and health-related quality of life of each subject (Appendix G)
- FACIT – Fatigue Scale (Appendix H)
- Work Instability Score for Rheumatoid Arthritis (RA-WIS) (Appendix I) is only required for those subjects who are currently working at the time that the questionnaire is administered
- EuroQoL-5D (EQ-5D) (Appendix J)

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

the subject's response. The patient reported outcome questionnaires will only be administered to patients and analyzed where a validated translation is available in their local language.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, questionnaires will be completed by the subject at the next feasible visit.

Medical and Surgical History

Any updates to the Medical and Surgical History will be obtained at the Baseline/Week 0 or at any visit during the study.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at scheduled study visits as specified in Table 2 prior to blood draws.

Body Weight

Body weight will be measured at all scheduled visits as specified in Table 2.

Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Table 2. Any physical examination abnormalities assessed by the investigator at Week 0 (Day 1) after first dose of study medication in Study M13-538 should be recorded as adverse events and captured on the appropriate eCRF in Study M13-538. All findings whether related to an adverse event or part of each subject's medical history will be captured on the appropriate eCRF page. Any physical examination abnormalities assessed by the investigator prior to the first dose of study medication should be recorded in Study M13-550 or Study M13-537 RCT as appropriate, as adverse events and captured on the appropriate eCRF.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, if a visit by phone or video conference occurs at one of the designated study visits specified to complete physical examination, the complete physical examination will be performed at the next feasible visit. A symptom-directed physical examination may be performed at any visits when necessary.

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

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

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, the Physician Global Assessment of Disease Activity will be completed by the physician at the next feasible visit.

Tender Joint Count (TJC) and Swollen Joint Count (SJC) Assessment

Tender Joint Count (TJC)

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

Swollen Joint Count (SJC)

An assessment of 66 joints (Appendix C) will be done by directed physical examination at visits specified in Table 2. The joints to be examined for swelling are the same as those

examined for tenderness, except the hip joints are excluded. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9") or no assessment ("NA").

If a patient receives an intra-articular injection during the study, the injected joint(s) should be scored as "NA = no assessment" for 90 days following injection.

If possible, the TJC and SJC should be performed by an independent joint assessor who should not perform any other study related procedures, as much as possible. In order to minimize variability, the same independent joint assessor should evaluate the subject at each visit for the duration of the trial. A back-up independent assessor, who is trained and competent in performing such assessments, should be identified. It is the responsibility of the Principal Investigator to ensure all assessors are qualified to perform joint assessments and that all training is documented. If the independent assessor is not available, the pre-identified back-up assessor will perform such assessments.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, the TJC and SJC will be performed at the next feasible visit by the independent joint assessor, if possible.

Pregnancy Test

- For women of childbearing potential, urine pregnancy test will be performed monthly at home between scheduled study visits. The results of these tests will be verbally communicated (via telephone) to the site. If a urine pregnancy test is positive, the subject must stop dosing, come in to clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory. A urine pregnancy test will be performed at all scheduled study visits as specified in Table 2, on all female subjects of childbearing potential. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive at any visit, withhold dosing and perform a serum pregnancy test for confirmation. The serum pregnancy test will be sent to and performed by the central laboratory. Pregnant subjects must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required.

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

Female subjects who are either postmenopausal, defined as:

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

and/or surgically sterile (bilateral oophorectomy or hysterectomy) are exempt from pregnancy testing.

In the event a urine pregnancy test may not be performed at the protocol specified visits due to study modifications related a state of emergency or pandemic situation like COVID-19, it can be performed by subjects at a local laboratory or it is possible for the Investigator to arrange a shipment from the study site directly to the subject's home of urine pregnancy test kits to have the urine pregnancy test done at home (see Section 5.3.1.1 - Sub-Section "Study Drug Dispensing, Dosing, and Compliance" for details). Home urine pregnancy test should be performed monthly, regardless of ability to obtain other laboratory samples.

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

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

TB Testing

For subjects with a negative QuantiFERON-TB Gold (or PPD) test at screening of the preceding RCT, an annual QuantiFERON-TB Gold (or protein purified derivative [PPD]) re-test will be required at visits indicated in Table 2. All subjects will be assessed for evidence of increased risk for TB by a questionnaire (Appendix L).

Subjects with a negative QuantiFERON®-TB Gold test OR negative PPD TB skin test AND no new evidence of increased TB risk based on the questionnaire may continue in the study.

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

If the QuantiFERON-TB Gold test is indeterminate, the QuantiFERON-TB Gold test should be performed locally (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the local testing result is negative, then the patient is considered to be negative.

- Interpretation of a positive annual TB test in low risk subjects: In cases where the QuantiFERON-TB Gold Plus test by the central laboratory is positive and the Investigator considers the subject at low risk for TB and has no clinical suspicion of TB, the Investigator may perform a local QuantiFERON-TB Gold Plus test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the Investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive or indeterminate, the test is considered positive.
- An equivalent Interferon Gamma Release Assay (IGRA) (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold Plus.

If one of the annual tests has a positive test result (seroconversion), a chest x-ray (CXR) needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Expert consultation can be considered per Investigator's discretion. Any positive TB screen after the patient has started the study should be reported as an adverse event (AE).

Subjects with evidence of active TB infection will be discontinued from the trial.

For subjects with seroconversion on an annual TB test, if a CXR cannot be done due to state of emergency or pandemic situation like COVID-19, the Investigator should contact the AbbVie TA MD to determine if the subject may continue on study drug. CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

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

Obtain a CXR for subjects with newly identified positive PPD or QuantiFERON-TB Gold test and every 48 weeks for subjects with TB risk factors as determined by the TB risk assessment form (Appendix H) or for subjects living in areas endemic for TB. Any positive TB test result after the subject has started study drug should be reported as an adverse event (AE).

The results of the TB test(s) will be retained at the site as the original source documentation.

TB Prophylaxis

If the subject has evidence of latent TB infection (newly positive TB test and the subject has a CXR not suggestive of active TB), prophylactic treatment must be initiated (per local guidelines). The prophylaxis needs to be completed.

Of note: Rifampicin or rifapentine is not allowed for TB prophylaxis

QuantiFERON-TB Gold Test

QuantiFERON-TB Gold test will be performed at visits specified in Table 2. The analyses will be performed by a certified laboratory.

OR

TB Skin Test

A PPD skin test (alternatively, also known as a TB Skin Test) will be performed as specified in Table 2 according to standard clinical practice. The TB Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration equal to or greater than 5 mm for RA subjects is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."

Chest X-Ray (CXR)

A CXR (posterior-anterior and lateral views) is required at the visits indicated in Table 2 for those subjects with new TB risk factors per the latent TB risk factor questionnaire (Appendix L), or for those subjects living in areas endemic for TB or for those subjects with a newly positive PPD or QuantiFERON-TB Gold. Subjects can have a CXR any time during the study as warranted based on the opinion of the Investigator.

A radiologist must perform an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the Principal Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, if a visit requires

completion of a CXR, the CXR will be performed at the next earliest feasible visit, unless the Investigator has determined, based on clinical judgement, that a CXR is required to ensure that it is safe to continue study drug administration. In this case, CXR should be performed as soon as restrictions allow at the study site or local hospital/facility.

12-Lead Electrocardiogram (ECG)

An ECG will be performed for all subjects at Weeks 0, 48, 96 and every 48 weeks afterwards (Wk 132, Wk 180, Wk 228 and Wk 276), until the end of the study or as clinically indicated during the study. An ECG may be administered at any time during the study based on the opinion of the Investigator.

Due to a state of emergency or pandemic situation like COVID-19, subject visits may be conducted via phone or video conference. In these situations, if a visit requires completion of an ECG, the ECG will be performed at the next earliest feasible visit, unless the Investigator has determined, based on clinical judgement, that an ECG is required to ensure that it is safe to continue study drug administration. In this case, the ECG should be performed as soon as restrictions allow at the study site or local hospital/facility.

hsCRP

Blood samples for high-sensitivity C-reactive protein (hsCRP) will be obtained at the time points specified in Table 2.

Pharmacokinetic (PK)

Blood collection will be performed at the scheduled study visits as specified in Table 2.

Clinical Laboratory Tests

Samples will be obtained at minimum for the clinical laboratory tests outlined in Table 3. A certified central laboratory will be utilized to process and provide results for the clinical

laboratory tests. All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

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

The fasting status will be recorded in the study source documentation.

If travel restrictions or other changes in local regulations due to state of emergency or pandemic situation like COVID-19 prevent the subject from having blood drawn for laboratory testing at the study site, it is possible for the Investigator to arrange for subjects to have laboratory work done at a local lab, hospital, or other facility to ensure the safety assessments are conducted per protocol. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator or designee as soon as possible and documented in the eCRF.

If laboratory samples cannot be obtained, study drug administration may be continued provided labs have been obtained within the prior 3 months, the investigator has reviewed the laboratory results and confirmed and discussed with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current lab results. The subject should be scheduled for laboratory draws as soon as feasible and no later than the next scheduled visit in order to continue the study drug administration.

If laboratory results are not available within the prior 3 months/two consecutive 12-week intervals, study drug dispensation is not allowed until the required laboratory tests are completed to ensure the safety assessments are conducted per protocol.

Blood and samples will be obtained for the laboratory tests as specified in Table 2. Blood draws should be performed after all clinical assessments and questionnaires (HAQ-DI, Patient's Assessment of Pain, FACIT, etc.), and vital sign determinations are obtained and before study drug administration during a visit.

Urine samples will be obtained for urinalysis testing as specified in Table 3. The central laboratory will be responsible for performing a macroscopic urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses defined as protein, ketones or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

Table 3. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis[a]	Other Laboratory Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Reticulocytes Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Creatinine Phospho-Kinase (CPK) Sodium Potassium Chloride Bicarbonate Calcium Inorganic phosphorus Uric acid Cholesterol LDL cholesterol HDL cholesterol Total protein Glucose Triglycerides Albumin INR (reflex only)[d]	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Microscopic examination, if needed	Serum pregnancy Test (Human Chorionic Gonadotropin [HCG])[b] High sensitivity C-reactive protein (hs-CRP) FSH[c]

a. A dipstick urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative.

b. Urine pregnancy test will be done at all scheduled clinic visits and at home between visits. Serum pregnancy test will be done if urine test is positive. Note that pregnancy tests are being performed only for women of childbearing potential.

c. FSH will be done to confirm post-menopausal status if age of the female is less than 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

d. INR will only be measured with a separate blood sample at repeat testing if ALT and/or AST > 3 × ULN.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range (Clinically Significant) value(s) to a satisfactory clinical resolution.

A laboratory test value(s) that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an adverse event.

Concomitant Medication

All concomitant medications and treatments are to be recorded in the appropriate eCRF as outlined in Section 5.2.3.

Enrollment and Assignment of Subject Numbers

Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria will keep the same subject number that they were assigned in Study M13-550 or Study M13-537.

Study Medication Dispensing, Dosing and Compliance

Study drug and Dosing Diary (Appendix K) will be dispensed to subjects beginning at the Baseline (Week 0) in this OLE study and at all scheduled and unscheduled study visits as specified in Table 2. No study medication will be dispensed at Final Visit. First dose of study medication will occur after all other Baseline (Week 0) procedures are completed. At each visit, the site personnel will review and copy the Dosing Diary and review the drug bottles to verify compliance. The dosing records, returned unused bottles and empty used bottles will be reviewed and verified for compliance at each visit by the research personnel at the study center. All relevant dosing information will be entered into the eCRF at each visit, as applicable.

(Refer to Section 5.5 for additional information).

Study drug may be shipped from the study site directly to the study subject's home due to study modifications related to a state of emergency or pandemic situation like COVID-19 if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Subject agrees to have the study drug shipped directly to their home
- Shipments may also include other study supplies (e.g., drug dosing diaries, in-home urine pregnancy test kits). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Optional Home Healthcare Service Due to State of Emergency or Pandemic Situation like COVID-19

Subjects may be offered the option of home healthcare visits provided by a study nurse or third-party vendor. Study procedures conducted in the home setting may include vital signs and body weight, physical exam, blood and urine samples collection, urine pregnancy test, adverse event and concomitant therapy assessment including compliance to contraception requirements if applicable, latent TB risk assessment form, review of subject dosing diary, TJC and SJC performed by the same independent joint assessor, if possible, to minimize variability.

This option can only be offered in countries and sites that comply with local regulatory and IRB/IEC requirements for homecare. Any pre-requisite submissions or notifications to the site IRB/IEC and local competent health authority should be made, and approvals must be obtained prior to implementation.

The investigator should be available via phone call if a consultation is necessary.

It is recommended that medical personnel entering a subject's home adhere to local health regulations during the COVID-19 pandemic, such as the use of Personal Protective Equipment (PPE), as required.

If the home visits will not be performed by site personnel, the site may be responsible for selecting a vendor, contracting with a vendor, and for ensuring continued compliance with the terms of the Clinical Study Agreement.

Individuals performing home visits need to be added to the delegation log.

5.3.1.2 Collection and Handling of Pharmacodynamic Variables

Instructions on preparation and shipment of pharmacodynamic samples will be provided by a certified laboratory or the sponsor outside this protocol.

5.3.1.3 Disease Response Biomarkers

Blood samples will be collected at time points specified in Table 2. The panel may include but is not limited to: IL-6, IL-1, TNFα, CXCL13, CXCL10, CRPM, C3M, C1M, MMP-3 and CTX-I. The fasting status will be recorded in the study source documentation. Separate instructions for the collection, handling and shipping of disease response biomarkers will be provided outside of the study protocol.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

A single pharmacokinetic sample will be collected at study visits BL, Weeks 6, 12, 24, 36, 48, 72, and 96 without regard to the time of dosing. Blood samples for PK will be collected at any time during the visit, and preferably within 1 to 8 hours after the last dose. The exact date, time and number of capsules of the last 2 doses of study drug taken prior to the pharmacokinetic sample collection will be recorded to the nearest minute starting with the dose prior to PK collection.

Blood samples for assay of upadacitinib will be collected in 3 mL K_2EDTA containing tubes by venipuncture. Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.2 Measurement Methods

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

5.3.3 Efficacy Variables

ACR20/50/70 response rates at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study will be evaluated based on 20/50/70% improvement in TJC, SJC, and ≥ 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Health Assessment Questionnaire Disability Index (HAQ-DI), and hsCRP. Change from Baseline in individual ACR components at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study will also be evaluated: TJC, SJC, Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, hsCRP, and Health Assessment Questionnaire Disability Index (HAQ-DI). Baseline data for each subject

will be the data collected at the visit immediately prior to starting treatment with active upadacitinib (this visit could be in RCT or OLE).

The proportion of subjects achieving Low Disease Activity (LDA) or Clinical Remission (CR), and the proportion of subjects achieving CR will be evaluated at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study. The criteria will be based on DAS28 [CRP] or CDAI as follows:

	DAS28 [CRP]	**CDAI**
LDA	$2.6 \leq$ to < 3.2	$2.8 <$ to ≤ 10
CR	< 2.6	≤ 2.8

Change from Baseline in DAS28 [CRP] disease activity score, CDAI and Patient Reported Outcomes including FACIT-Fatigue Scale, RA-WIS, and EQ-5D will be analyzed at Weeks 6, 12, 24, 36, 48, 72, 96 and every 24 weeks thereafter until the end of the study.

5.3.4 Safety Variables

Incidence of adverse events, changes in vital signs, physical examination results and clinical laboratory data will be assessed throughout the study.

5.3.5 Pharmacokinetic Variables

Plasma upadacitinib concentrations will be determined at the times indicated in Table 2. A mixed-effects modeling approach may be used to estimate the population central value and the empirical Bayesian estimates of the individual values for upadacitinib oral clearance (CL/F) and volume of distribution (V_{ss}/F). Additional parameters may be estimated if useful in the interpretation of the data.

5.3.6 RA Disease Response Biomarkers Variables

Subjects will have additional blood samples collected to assess disease response. Samples will be analyzed for measurement of non-genetic markers related to disease

activity/prognosis of RA, autoimmunity/inflammation, and/or response to upadacitinib. The panel may include but is not limited to: IL-6, IL-1, TNFα, CXCL13, CXCL10, CRPM, C3M, C1M, MMP-3 and CTX-I.

Change from Baseline in RA disease response biomarkers at Weeks 6, 12, 24 and 48 will be evaluated.

5.3.7 Pharmacodynamic Variables

In-Vivo Biomarkers

Blood samples will be collected to assess JAK activity effects on certain lymphocyte subsets including T (CD4+ and CD8+), B, NK, NKT, reticulocyte and other cell types.

Change from Baseline in in-vivo pharmacodynamic biomarkers at Weeks 6, 12, 24 and 48 will be evaluated.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol.

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

- Clinically significant abnormal laboratory results or adverse events, which rule out continuation of the study medication, as determined by the Investigator and the AbbVie Therapeutic Area Medical Director.
- Serious infections (e.g., sepsis) which would put the subject at risk for continued participation in the trial as determined by the Investigator in consultation with the AbbVie Therapeutic Area Medical Director.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from study drug or the study.

- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Therapeutic Area Medical Director.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie SDP.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study medication.
- Subject has known malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease (including myelitis).
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation as determined by the Investigator.
- Subject has failed to achieve at least 20% improvement from Baseline (RCT period) in TJC and SJC with upadacitinib as described in Section 5.1.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.
- Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injury).

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the premature discontinuation visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation and preferably prior to the initiation of another therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final visit (a telephone call is sufficient if a site visit is not possible) will occur for all subjects participating in the OLE study, approximately 30 days after the last dose of study medication to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the Investigator to ensure subject safety and continuity of care.

During a state of emergency or pandemic situation like COVID-19, the Investigator should contact the sponsor TAMD before discontinuing a subject from the study or study drug for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

All attempts must be made to determine the date of the last study drug dose and the primary reason for premature discontinuation. The information will be recorded on the appropriate eCRF page.

For subjects that are considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, two phone calls must be made and one certified letter must be sent and documented in the subject's source documentation.

Subjects who discontinue the study prematurely will not be replaced.

5.4.2 Discontinuation of Entire Study

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

notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Treatments administered during this OLE include upadacitinib 6 mg BID, 12 mg BID, (15 mg QD or 30 mg QD from January 2017). All subjects start treatment with 6 mg BID. Dose adjustments are allowed as described in Section 5.1.

Subject receiving 6 mg BID will dose with two 3 mg capsules twice a day.

Subjects receiving 12 mg BID will dose with one 12 mg capsule twice a day.

Subject receiving 15 mg QD will dose with one 15 mg tablet once a day.

Subject receiving 30 mg QD will dose with one 30 mg tablet once a day.

Study drug will be taken orally beginning at Baseline/Week 0 in OLE. Subjects will be instructed to take study drug at approximately the same times each day. The study drug can be taken with or without food. Subjects will continue their weekly stable dose of MTX and folic acid. AbbVie will not supply MTX or folic acid.

If a subject is unable to come to the study site to pick up their study drug due to state of emergency or any pandemic like COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to Section 5.3.1.1 for details on DTP shipment of study drug.

Information about the Investigational Product is presented in Table 4.

Table 4. Identity of Investigational Products

Investigational Product	Upadacitinib	
Mode of Administration	Oral	Oral
Dosage Form	Capsule	Capsule
Strength (mg)	3	12
Mode of Administration	Oral	Oral
Dosage Form	Film coated Tablet	Film coated Tablet
Strength (mg)	15	30

5.5.1.1 Packaging and Labeling

Upadacitinib will be packaged in bottles containing 100 capsules or 100 tablets per bottle. Each bottle (kit) label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements.

Labels must remain affixed to the bottles (kits) and must not be concealed by any over-labeling. All blank spaces on the label will be completed by site staff prior to dispensing to the subjects.

5.5.1.2 Storage and Disposition of Study Drugs

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

5.5.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. The upadacitinib treatment is the same for all subjects so that there is no assignment of subjects to treatment groups. As a subject is confirmed for Baseline (Week 0) in OLE to be appropriate for participation in the study, the site will

enter the subject's number from Study M13-550 or Study M13-537, based on which study the subject was enrolled in, into IVRS (Interactive Voice Response System)/IWRS (Interactive Web based Response System) to obtain study drug. All eligible subjects will be assigned to upadacitinib 6 mg BID immediately after or up to 30 days following the Last Visit (Week 12) of Study M13-550 or Study M13-537 using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS/IWRS will be provided to each site. From Week 6 in OLE, subjects will receive subsequent treatment as described in Section 5.5.1.

5.5.3 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in Section 5.5.1.

On scheduled study visit days, subject should follow their regular routine for study drug administration.

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

Capsule Formulation:

If a subject should forget to take his/her study drug dose at his/her regularly scheduled dosing time, he/she should take the forgotten dose as soon as he/she remembers the dose was missed as long as it is at least 6 hours before his/her next scheduled dose. If a subject only remembers the missed dose within 6 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.

Tablet Formulation:

If a subject should forget to take his/her study drug dose at his/her regularly scheduled dosing time, he/she should take the forgotten dose as soon as he/she remembers the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject

only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.

If the subject experiences a study drug interruption > 30 days, they should notify their investigator, and the investigator will determine if study drug should be restarted or if the subject should be discontinued from the study.

Subjects who, in the opinion of the Investigator, develop adverse events that require study drug interruption and/or reach protocol specified toxicity management thresholds can have the study drug interrupted for up to 30 days while recovering from the adverse event.

5.5.4 Blinding

This is an open-label study.

5.5.5 Treatment Compliance

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

Subject dosing will be recorded on a subject dosing diary (Appendix K). Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. The study site personnel will document compliance in the study source documents. Subjects will be counseled on missed doses of medication. If the subject does not return the dosing diary, used and unused study drug bottles the site should question the subject and obtain as much information as possible as to the dosing of the study drug.

The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the dosing diary is returned before completing on the applicable eCRF page.

5.5.6 Drug Accountability

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

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

All empty/used study drug packaging will be inventoried by the site. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary. Site staff will complete study drug accountability via IRT by using source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible. After drug accountability and monitor reconciliation has been completed, used packaging and unused study drug will be destroyed on site according to local procedures or regulations or returned to the destruction depot (for those sites that do not meet AbbVie's documentation requirements for on-site destruction). The use of a third party vendor for drug destruction must be preapproved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

Monitors will reconcile the site's processes, source documents, subject's dosing diaries, IRT or site accountability records, and destruction records to assure site compliance.

5.6 Discussion and Justification of Study Design

Subjects who have completed Study M13-550 or Study M13-537 RCT with upadacitinib will be allowed to enroll in the OLE study to continue to receive upadacitinib for up to approximately 312 weeks. The primary objective of OLE study is to collect long-term

safety and tolerability data for upadacitinib. All subjects who roll over into the OLE will be assigned to upadacitinib 6 mg BID initially, regardless of treatment assignment during RCT period, and the basis of this design is to preserve the blinding of treatment assignment in the RCT period. All subjects assigned to 6 mg BID initially will have an option to increase the dose to 12 mg BID (or 30 mg QD from January 2017) throughout the treatment period if a subject is unable to achieve low disease activity with upadacitinib 6 mg BID. At any time during the treatment period, the upadacitinib dose can be decreased back to 6 mg BID (or 15 mg QD from January 2017) per Investigator's judgment if there are safety and tolerability concerns. Those subjects who are unable to achieve at least 20% improvement in both SJC and TJC (minimum clinical efficacy) at defined time-points will be permanently discontinued. This design allows for collection of long-term safety data and avoids continued treatment of those subjects who do not respond to study medication.

From January 2017, all subjects who are at Week 72 or beyond will receive once-daily tablet formulation (15 mg QD or 30 mg QD). Preliminary results of a bioequivalent study demonstrated that single 15 mg and 30 mg doses of the once-daily formulation provide comparable AUC, but significantly lower C_{max} than single doses of 12 mg immediate release (IR) formulation (equivalent to 6 mg BID dose) and 24 mg IR formulation (equivalent to 12 mg BID dose), respectively. At steady-state, the once-daily dose of 15 mg QD is predicted to achieve comparable daily AUC, lower or comparable C_{max}, and comparable C_{trough} to 6 mg BID IR formulation, and the once-daily dose of 30 mg QD is predicted to be equivalent to 12 mg BID IR.

Subjects who are on 6 mg BID (IR) capsule dosing will be transitioned to 15 mg QD tablet dosing. Subjects who are on 12 mg BID dosing will be transitioned to 30 mg QD dosing. Capsule formulation will not be available to the subjects after transition to tablet formulation.

Starting with Amendment 5, subjects who are receiving 30 mg QD open-label upadacitinib will have the option to decrease to the 15 mg QD dose based on investigator's discretion.

5.6.1 Appropriateness of Measurements

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

5.6.2 Suitability of Subject Population

This OLE study will enroll subjects who have completed Study M13-550 or Study M13-537 RCT with upadacitinib. Only those subjects who have met all of the specified inclusion and none of the exclusion criteria will have an option to enter into the OLE study to receive upadacitinib, as long as the subject is willing and the Investigator believes that continuing the therapy with upadacitinib is appropriate.

5.6.3 Selection of Doses in the Study

All subjects will be assigned to upadacitinib 6 mg BID at the beginning of OLE study. During the course of OLE treatment period the upadacitinib dose can be increased to 12 mg BID based on clinical efficacy assessment and as long as the Investigator has no safety concerns. From January 2017, all subjects who are at Week 72 or beyond will receive once-daily tablet formulation. Subjects who are on 6 mg BID dosing will be transitioned to 15 mg QD dosing. Subjects who are on 12 mg BID dosing will be transitioned to 30 mg QD dosing. The capsule formulation will not be available to subjects once the transition to tablet formulation has occurred.

The change in dose selection in this study is based on extrapolation of pre-clinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the Phase 1 studies in healthy volunteers (single and multiple ascending dose Studies M13-401 and M13-845, respectively) and completed Phase 2b randomized, controlled studies (RCTs) in RA subjects (Studies M13-537 and M13-550). The doses selected, 15 mg QD and 30 mg QD, are expected to approximate the exposures achieved with the 6 mg BID and 12 BID immediate release formulations, respectively, which

should be efficacious with an acceptable safety profile. Preliminary results from an ongoing relative bioavailability study demonstrated that single 15 mg and 30 mg doses of the once-daily formulation provide comparable AUC and significantly lower C_{max} than single doses of 12 mg immediate release (IR) formulation (AUC equivalent to 6 mg BID dose tested in Phase 2) and 24 mg IR formulation (AUC equivalent to 12 mg BID dose tested in Phase 2), respectively, under fasting conditions. At steady-state, the once-daily dose of 15 mg QD is predicted to achieve comparable daily AUC and C_{max}, and non-inferior C_{trough} to 6 mg BID IR formulation. In the Phase 2 RCTs, the 6 mg BID dose was shown to achieve the near maximum efficacy. The once-daily dose of 30 mg QD is predicted to achieve comparable daily AUC and C_{max}, and non-inferior C_{trough} to 12 mg BID IR formulation. In the Phase 2 RCTs, the 12 mg BID dose was clearly shown to achieve the plateau of efficacy.

Study drug will be given for approximately 312 weeks and will not exceed a dose of 30 mg daily.

6.0 Adverse Events

6.1 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2). For adverse events, please refer to Section 6.1 through Section 6.9.

6.2 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record

any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.3 Definitions

6.3.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section 6.10 regarding toxicity management]) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and

the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.3.2 Serious Adverse Events

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

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

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

6.4 Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study (see detailed toxicity management in Section 6.10):

- Serious infections, opportunistic infections, herpes zoster, and active TB;
- Malignancy (all types);
- Adjudicated Gastrointestinal perforations;
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Anemia;
- Neutropenia;
- Lymphopenia;
- Increased serum creatinine and renal dysfunction;
- Hepatic events and increased hepatic transaminases;
- Increased creatine phosphokinase (CPK);

- Adjudicated cardiac, embolic and thrombotic events (non-cardiac, non-CNS).

6.5 Adverse Event Severity

The Investigator will classify adverse events according to the Rheumatology Common Toxicity Criteria v.2.0 (Appendix M).[10]

6.6 Relationship to Study Drug

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

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

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

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

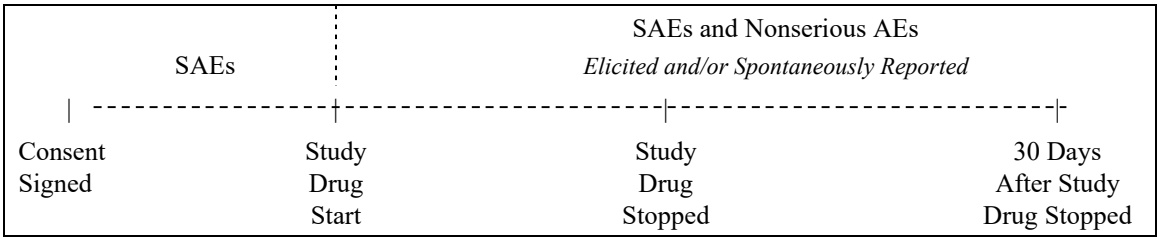
6.7 Adverse Event Collection Period

All adverse events reported from the time of study drug administration (Day 1) until 30 days following discontinuation of study drug administration will be collected, whether

solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2, and recorded on the appropriate eCRFs.

Figure 2. Adverse Event Collection



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

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

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures (SAE Supplemental Procedure eCRF);
- Hepatic;
- Renal;
- Herpes Zoster Infection;
- CPK increases considered by the investigator to be an AE;
- Embolic and thrombotic events (non-cardiac, non-CNS);
- COVID-19

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

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above.

The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events):

- COVID -19 Supplemental Signs/ Symptoms
- COVID-19 Status Form

6.8 Serious Adverse Event Reporting

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

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847)-938-0660

For safety concerns, contact the Immunology Safety Team at:

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

Toll Free: +1 (833) 942-2226
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

Therapeutic Area Medical Director:

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

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

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

Phone: +1 (973) 784-6402

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

6.9 Pregnancy

Pregnancy in a study subject or the partner of an enrolled subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected after obtaining proper consent.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

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

6.10 Toxicity Management

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

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or a serious opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As

appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated. If study drug administration is interrupted for more than 30 days, the subject should be discontinued from the study. Subjects who develop active tuberculosis must be permanently discontinued from study drug.

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

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

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

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

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

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

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

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

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment, following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 5 (confirmation by repeat testing is required) and may require an appropriate supplemental eCRF to be completed. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 5, the repeat testing must occur as soon as possible.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1,000/µL, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
Absolute lymphocytes counts (ALC)	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total white blood cell count*	• If confirmed < 2,000/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its Baseline value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its Baseline value.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5. o A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample and contact the TAMD. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug • For subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within one week: o ALT > 5 × ULN OR o ALT or AST > 3 × ULN if an alternative cause is not readily identified. • A positive result for HBV DNA PCR testing in these subjects will require immediate interruption of study drug and a hepatologist consultation should occur within one week for recommendation regarding subsequent treatment. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and >ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × baseline value and ≤ ULN • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. • For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
Creatine Phosphokinase	• If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie Therapeutic Area Medical Director. • For the above CPK elevation scenarios, complete supplemental CPK eCRF.

* Local requirements may apply. Refer to Appendix N for local requirements (United Kingdom).

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

6.11 Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess cardiovascular and embolic and thrombotic (non-cardiac, non-CNS) adverse events as defined by the Cardiac Adjudication Committee charter.

6.12 Product Complaint

6.12.1 Definition

A Product Complaint is any Complaint (see Section 6.1 for the definition) related to the biologic or drug component of the product.

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

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

6.12.2 Reporting

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

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 or any pandemic or any state of emergency situation) after a subject has been enrolled, the

principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned clinical monitor, or AbbVie representative, or the following AbbVie clinical study team contact(s):

Primary Contact:

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

Office: [redacted]
Cell:
Fax:
Email:

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

Examples of protocol deviations include the following:

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 Dataset for Analysis

The analysis set consists of all subjects who enrolled into this OLE study and received at least one dose of open-label study medication upadacitinib. This analysis set will be the primary analysis population for both efficacy and safety evaluation.

8.1.2 Subject Accountability

The number of subjects who received at least one dose of study drug, the number of subjects who completed the study, and the number of subjects who prematurely discontinued will be calculated overall and for each investigational site.

8.1.3 Baseline Characteristics

For analyses purposes, baseline data for each subject will be the data collected at the visit immediately prior to starting double-blind treatment. In an alternate assessment for summarizing the safety and laboratory data, baseline data will be assumed to be the data collected at the visit immediately prior to starting treatment with active upadacitinib.

Demographic variables such as age, gender, race, height, weight, BMI, race, ethnicity, duration of disease, vital signs (blood pressure, heart rate, and temperature), and planned efficacy assessments such as the counts for both SJC and TJC, Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Physical Function by Heath Assessment Questionnaire – Disability Index (HAQ-DI), and hsCRP will be summarized at Baseline.

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

8.1.4 Subject Disposition and Study Drug Exposure

8.1.4.1 Subject Disposition

The number and percentage of subjects who are enrolled and received at least one dose of study drug, and the number of subjects who prematurely discontinued and the reason for premature discontinuation will be summarized. Premature discontinuation of study drug will be summarized, with frequencies and percentages overall and by reason for discontinuation for all subjects who received at least one dose of study drug. Subjects may have multiple reasons for prematurely discontinuing study drug, but will be counted no more than once for the total ("Any Reason").

8.1.4.2 Study Drug Exposure

Extent of exposure to study drug will be summarized for all subjects who received at least one dose of open-label study drug in Study M13-538. The duration (days) of study drug treatment in both open-label treatment period and combined RCT (Study M13-550 or Study M13-537) plus open-label treatment period will be summarized with the mean, standard deviation, median and range.

8.1.5 Efficacy Analysis

8.1.5.1 Efficacy Variables

The efficacy endpoints of this study include the ACR20/50/70 response rates at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study.

A subject will be considered an ACR20/50/70 responder if:

1. The counts for both SJC and TJC have reduced from Baseline by 20/50/70% or more; and
2. At least three of the five remaining ACR core set measures show reduction of 20/50/70% or more in baseline assessment:
    - Patient's Assessment of Pain (VAS),

- Patient's Global Assessment of Disease Activity,
- Physician's Global Assessment of Disease Activity,
- Patient's Assessment of Physical Function by Heath Assessment Questionnaire – Disability Index (HAQ-DI),
- hsCRP.

Other efficacy endpoints of this study are:

- Individual components of ACR at every scheduled study visit (Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until end of the study):
  - TJC
  - SJC
  - Patient's Global Assessment of Disease Activity
  - Physician's Global Assessment of Disease Activity
  - Patient's Assessment of Pain
  - hsCRP
  - Health Assessment Questionnaire Disability Index (HAQ-DI)
- Proportion of subjects achieving low disease activity (LDA) or clinical remission (CR) based on DAS28 [CRP] or CDAI criteria respectively at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study.
- Proportion of subjects achieving CR at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study.
- Change from Baseline in DAS28 [CRP] at Weeks 6, 12, 24, 36, 48, 72, 96 and every 24 weeks thereafter until the end of the study.
- Change from Baseline in CDAI at Weeks 6, 12, 24, 36, 48, 72, 96 and every 24 weeks thereafter until the end of the study.
- Change from Baseline in Patient Reported Outcomes at Weeks 6, 12, 24, 36, 48, 72, 96 and every 24 weeks thereafter until the end of the study:
  - FACIT – Fatigue Scale,

- Work Instability Scale for RA (RA-WIS),
- EuroQoL-5D (EQ-5D).

The proportion of subjects achieving Low Disease Activity (LDA) or Clinical Remission (CR), and the proportion of subjects achieving CR will be evaluated at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study. The criteria will be based on DAS28 [CRP] or CDAI as follows:

	DAS28 [CRP]	**CDAI**
LDA	2.6 ≤ to < 3.2	2.8 < to ≤ 10
CR	< 2.6	≤ 2.8

DAS28 [CRP] score will be determined based on a continuous scale of combined measures of TJC, SJC, Patient's Global Assessment of Disease Activity (PtGA) (in mm), and hsCRP (in mg/L).

$$\text{DAS28 [CRP]} = 0.56\ \sqrt{(\text{"TJC28"})} + 0.28\ \sqrt{(\text{"SJC28"})} + 0.36\ \ln(\text{CRP} + 1) + 0.014\ \text{PtGA} + 0.96,$$

where √ is square root and ln is natural log. A score > 5.1 generally means high disease activity; 2.6 ≤ DAS28 [CRP] < 3.2 generally means low disease activity (LDA); DAS28 [CRP] < 2.6 is generally considered clinical remission (CR).

Clinical Disease Activity Index (CDAI) is a composite index (without CRP) for assessing disease activity. CDAI is based on the simple summation of the counts of SJC28 and TJC28 along with Patient's Global Assessment (VAS [0 – 10 cm]) (PtGA) and Physician's Global Assessment (VAS [0 – 10 cm]) (PhGA) for estimating disease activity.

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

% Improvement in Joint Count from Baseline in RCT = [(Number of Swollen/Tender Joints at Day 1 of RCT – Number of Swollen/Tender Joints at Current Visit)/Number of Swollen/Tender Joints at Day 1 of RCT]*100

In this study, the level of disease activity is interpreted as remission (CDAI ≤ 2.8), low (2.8 < CDAI ≤ 10), moderate (10 < CDAI ≤ 22), or high (CDAI > 22).

8.1.5.2 Efficacy Analysis

The efficacy analyses will be conducted with the analysis set described in Section 8.1.1 and the observed cases (OC). The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

Frequencies and relative frequencies (percentages) of ACR20/50/70 will be summarized with 95% confidence intervals at each post-baseline time point.

The proportion of subjects achieving Low Disease Activity (LDA) or Clinical Remission (CR), and the proportion of subjects achieving CR will be evaluated at Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96 and every 24 weeks thereafter until the end of the study. Frequencies and relative frequencies will be reported with 95% confidence intervals by visit, and will be summarized based on DAS28 [CRP] and CDAI criteria respectively.

For each of the change from baseline measurement, namely, TJC, SJC, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Pain (VAS), HAQ-DI, hsCRP, DAS28 [CRP] disease activity score, and CDAI, the mean, standard deviation, median, and range will be reported at each post-baseline time point. For Patient Reported Outcomes variables including change from baseline analyses of FACIT, RA-WIS, and EQ-5D, the mean, standard deviation, median and range will be summarized by visit. Confidence intervals at an overall level of 95% will be provided.

The impact of time between completion of RCT and roll-over to OLE will be explored.

8.1.5.3 Multiple Comparisons

Not applicable.

8.1.6 Safety Analysis

8.1.6.1 General Considerations

All subjects who receive at least one dose of upadacitinib in this OLE study will be included in the safety analysis. Incidence of adverse events, serious adverse events, premature discontinuation, and changes from Baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed by visit. Treatment-emergent adverse events will be tabulated by system organ class and by MedDRA preferred term. Mean change from Baseline for laboratory and vital signs data will be summarized by visit. For analyses purposes, baseline for vital signs, physical examination results, and clinical laboratory results for subjects will be the data collected at the visit immediately prior to starting double-blind treatment. In an alternate assessment for summarizing the safety and laboratory data, baseline data will be assumed to be the data collected at the visit immediately prior to starting treatment with active upadacitinib.

Incidence of adverse events, changes in vital signs, physical examination results, and clinical laboratory values will be analyzed.

Treatment emergent adverse events will be tabulated by system organ class (SOC) and by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Mean change from baseline for laboratory and vital signs data will be summarized by visit.

Missing safety data will not be imputed.

The impact of time between completion of RCT and roll-over to OLE will be explored.

8.1.6.2 Analysis of Adverse Events

8.1.6.2.1 Treatment-Emergent Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent adverse events, defined as AEs that began or worsened in severity after initiation of open-label study drug upadacitinib in

this OLE study, will be tabulated by system organ class (SOC) and MedDRA preferred term.

Adverse events starting more than 30 days following discontinuation of study drug will not be included in summaries of treatment-emergent AEs. Adverse events starting more than 30 days following discontinuation of study drug will be summarized separately as post-treatment AEs.

When summarizing adverse events by relationship or severity, if a subject has an event with unknown severity or relationship then the subject will be counted in the severity/relationship categories of "unknown" even if the subject has a second occurrence of the same event with a severity/relationship present. The only exception is if the subject has a second occurrence of the same event with the most extreme severity (i.e., "severe") or a relationship category of "reasonable possibility." In this case, the subject will be counted under these most extreme severity/relationship categories.

The AEs of special interest (including but not limited to serious infection, opportunistic infection, herpes zoster, TB, gastrointestinal perforations, malignancies, MACE, renal dysfunction, anemia, increased CPK, drug-related hepatic disorders and thrombotic and embolic events) will be summarized.

Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe incident in each study period. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

Frequencies and percentages of subjects with treatment-emergent AEs will be summarized as follows:

- Any event
- By system organ class, and preferred term
- By system organ class, preferred term and maximum relationship

- By system organ class, preferred term and maximum severity
- Any event and by system organ class and preferred term for events resulting in death
- Any event and by system organ class and preferred term for events resulting in study drug discontinuation
- Any event and by system organ class and preferred term for serious events
- Any event and by system organ class and preferred term for adverse events with a relationship of "reasonable possibility"
- Any event and by system organ class and preferred term for adverse events of special interest

All AEs leading to premature discontinuation of study drug will be presented in listing format.

A listing of treatment-emergent AEs grouped by SOC and MedDRA preferred term with subject ID numbers will be generated.

The post-treatment AEs will be summarized in the same way as the treatment-emergent AEs described above.

8.1.6.2.2 Serious Adverse Events and Death

All treatment-emergent serious adverse events, adverse events leading to death, and adverse events leading to discontinuation will also be presented in listing format. In addition, SAEs will be summarized by SOC and MedDRA preferred term.

8.1.6.3 Analysis of Laboratory and Vital Sign Data

Changes from baseline to minimum value, maximum value and final values in continuous laboratory and vital sign parameters will be summarized.

Vital signs and laboratory data will be described by statistical characteristics and frequency of abnormal values. Frequencies and percentages of subjects with laboratory shifts from baseline to the final values using normal ranges to define categories (low,

normal, high, and missing) will be summarized by the respective categories. Values beyond the normal values will be listed. Low or high laboratory values will also be flagged in the data listings.

8.1.7 Pharmacokinetic and Exposure-Response Analyses

Individual upadacitinib plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods. Upadacitinib pharmacokinetics may be evaluated using population PK modeling approach. The relationship between upadacitinib exposure and clinical efficacy or safety response(s) may be explored. The data from this study may be combined with the data from other studies of upadacitinib for the exposure-response analysis. Data from this study may not be analyzed separately. Results of the population PK and exposure-response analyses may be presented in a separate report prior to regulatory filing of upadacitinib for treatment of RA.

Additional analyses will be performed if useful and appropriate.

8.1.8 Statistical Analysis of Biomarker Data

Summary statistics for the pharmacodynamic biomarkers and disease response biomarkers at baseline and post-treatment time points, in addition to change from baseline at each time will be provided; this will include mean, standard deviation, median, quartiles, and range for each group. Appropriate graphical visualizations such as association of each biomarker to the relevant efficacy endpoints, pairwise correlations between biomarkers, trellis/3D plots that condition on baseline factors, etc., will be provided. The association of biomarkers to the efficacy and safety endpoints will be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling algorithms. Pairwise correlations and graphical summaries will be provided. Optimal multivariate combinations of biomarkers that associate with efficacy endpoints, subject response/non-response (with respect to appropriate clinical endpoints), and also with safety endpoints will be explored via a variety of statistical predictive modeling algorithms. Also cut-points for individual biomarkers and optimal combinations of biomarkers that differentiate the subject response with respect to efficacy/safety endpoints

will be explored. The significance of these multivariate combinations of biomarkers will be assessed via at least 20 iterations of 5-fold cross-validation.

8.1.9 Interim Analysis

Interim analyses may be performed, as appropriate, to help plan future studies.

8.2 Determination of Sample Size

It is anticipated that up to 500 subjects will be enrolled in this OLE study.

9.0 Ethics

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

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

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

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that

affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

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

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

9.3 Subject Information and Consent

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

Procedures for the Prevnar 13® pneumococcal vaccine sub-study will only be performed if the subject has voluntarily provided written informed consent for this sub-study, approved by an IRB/IEC, and after the nature of these activities has been explained and the subject has had an opportunity to ask questions. This written consent must be signed before the sub-study activities are performed. If the subject does not consent to the sub-study, it will not impact the subject's participation in the main study.

Due pandemic situation like COVID-19 or state of emergency, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

During the COVID-19 pandemic or any pandemic/state of emergency, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10.2 Case Report Forms

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the

investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

The adverse events electronic data capture eCRF data segments of: alternative etiology, severity, frequency and relationship to study drug, may also be used as source and will require Investigator approval on the eCRF.

Electronic Patient Reported Outcomes (ePRO)

Patient reported data must be completed for each subject enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) tool called Trialmax, provided by the technology vendor CRF Health of Lansdale, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO tool is available through the vendor, CRF Health, while the user acceptance testing of the study-specific ePRO design will be conducted and maintained at AbbVie.

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

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

The ePRO data will be collected electronically via a tablet device into which the subject and physician will record required information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for patients or physician to complete more than one of the same assessments at any one visit. Data entered on the device will be immediately stored to the device itself and

automatically uploaded to a central server maintained and managed by CRF Health. The investigator and delegated staff will be able to access all uploaded subject data via a password-protected website up until the generation, receipt and confirmation of the study archive.

The following assessments will be completed by the subject or physician in Electronic Patient-Reported Outcome (ePRO) device:

- Physician's Global Assessment of Disease Activity VAS
- Joint Evaluation Worksheet (Tender Joint Count and Swollen Joint Count)
- Patient's Global Assessment of Disease Activity VAS
- Patient's Assessment of Disease Pain VAS
- HAQ-DI Questionnaire
- Work Instability Scale for RA (RA-WIS)
- FACIT – Fatigue Scale
- EuroQol-5D (EQ-5D)

10.3 Data Collection Process

AbbVie is using an ePRO tool to capture portions of the clinical data defined in this protocol. The use of ePRO requires certain process changes compared to the use of traditional paper patient reported outcomes. Trial-Specific Guidelines have been developed to document changes from the traditional paper patient reported outcomes process. These Trial-Specific Guidelines govern the ePRO processes in this trial.

11.0 Data Quality Assurance

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

12.0 Use of Information

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

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

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

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

13.0 Completion of the Study

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

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

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

14.0 Investigator's Agreement

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

Protocol Title:	Phase 2 Study, Multicenter, Open-Label Extension (OLE) Study in Rheumatoid Arthritis Subjects who have Completed a Preceding Phase 2 Randomized Controlled Trial (RCT) with Upadacitinib (ABT-494)
Protocol Date:	01 December 2020

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

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

Appendix C. Joint Evaluation Worksheet Example

JOINT EVALUATION												
	Subject Right						Subject Left					
	1 = Present 0 = Absent				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
JOINT (Tick Correct Answer)	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
1. Temporomandibular	0	1	0	1	9	NA	0	1	0	1	9	NA
2. Sternoclavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
3. Acromio-clavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
4. Shoulder	0	1	0	1	9	NA	0	1	0	1	9	NA
5. Elbow	0	1	0	1	9	NA	0	1	0	1	9	NA
6. Wrist	0	1	0	1	9	NA	0	1	0	1	9	NA
7. Metacarpophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
8. Metacarpophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
9. Metacarpophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
10. Metacarpophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
11. Metacarpophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
12. Thumb Interphalangeal	0	1	0	1	9	NA	0	1	0	1	9	NA
13. Prox. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
14. Prox. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
15. Prox. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
16. Prox. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
17. Distal Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
18. Distal Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
19. Distal Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
20. Distal Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
21. Hip	0	1	--	--	9	NA	0	1	--	--	9	NA
22. Knee	0	1	0	1	9	NA	0	1	0	1	9	NA
23. Ankle	0	1	0	1	9	NA	0	1	0	1	9	NA
24. Tarsus	0	1	0	1	9	NA	0	1	0	1	9	NA
25. Metatarsophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
26. Metatarsophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA

JOINT EVALUATION												
	Subject Right						Subject Left					
	1 = Present 0 = Absent				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
JOINT (Tick Correct Answer)	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
27. Metatarsophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
28. Metatarsophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
29. Metatarsophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
30. Great Toe/Hallux	0	1	0	1	9	NA	0	1	0	1	9	NA
31. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
32. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
33. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
34. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA

Appendix D. Physician's Global Assessment of Disease Activity Example

Visual Analog Scale (VAS)

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

- P*hysician's global assessment of disease activity (current status)*
  The Physician will rate global assessment of subject's current disease activity ranging from 0 to 100 (see example below)

Mark the line below to indicate the subject's rheumatoid arthritis disease activity (independent of the subject's self-assessment).

0		100
Very Low		Very High

Appendix E. Patient's Global Assessment of Disease Activity Example

Visual Analog Scale (VAS)

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

- *Patient's global assessment of disease activity (within last 24 hours)*
  The subject will rate the severity of the RA symptoms and how he/she is doing from 0 to 100. This assessment will be used for the DAS28 [CRP] calculation in this study (see example below):

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

0		100
Very Well		Very Poorly

Appendix F. Patient's Assessment of Pain Example

Visual Analog Scale (VAS)

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

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

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

NO PAIN	———————————————————	**WORST POSSIBLE PAIN**

Appendix G. Health Assessment Questionnaire (HAQ-DI) Example

HEALTH ASSESSMENT QUESTIONNAIRE

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

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

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING AND GROOMING				
Are you able to:				
Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Cane
☐ Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.)
☐ Walker
☐ Built up or special utensils
☐ Crutches
☐ Special or built up chair
☐ Wheelchair
☐ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and Grooming
☐ Eating
☐ Arising
☐ Walking

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

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open jars which have been previously opened?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom
☐ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- ☐ Hygiene
- ☐ Gripping and opening things
- ☐ Reach
- ☐ Errands and chores

HAQ – United States/English

HAQ-DI_AU1.0-eng-USori.doc

Appendix H. FACIT – Fatigue Scale Example

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix I. Work Instability Scale for Rheumatoid Arthritis (RA-WIS) Example

Work Instability Score For Rheumatoid Arthritis

On the following page you will find some statements, which have been made by people who have rheumatoid arthritis. We would like you to tick "yes" if the statement applies to you, and tick "no" if it does not. Please choose the response that applies best to you at the moment.

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

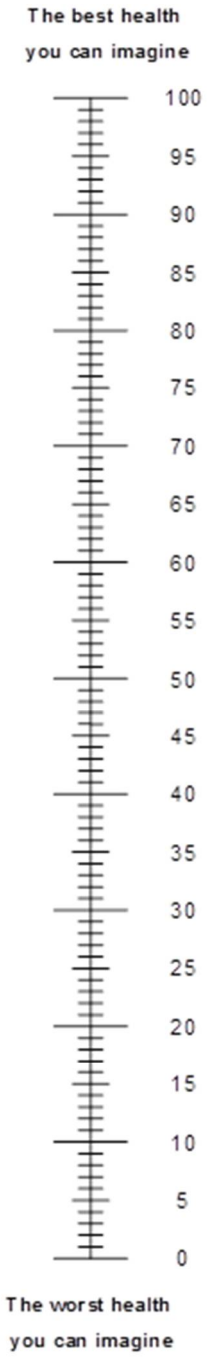
Appendix J. EuroQoL-5D Example

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

Mobility	
I have no problems walking	☐
I have slight problems walking	☐
I have moderate problems walking	☐
I have severe problems walking	☐
I am unable to walk	☐
Self-Care	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
Usual Activities ***(e.g., work, study, housework, family or leisure activities)***	
I have no problems with doing my usual activities	☐
I have slight problems with doing my usual activities	☐
I have moderate problems with doing my usual activities	☐
I have severe problems with doing my usual activities	☐
I am unable to do my usual activities	☐
Pain/Discomfort	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
Anxiety/Depression	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

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

YOUR HEALTH TODAY = ☐



Appendix K. Dosing Diary Example

Subject Number: _____

Investigator, Dr: _____

Phone Number: _____

While dosing outside of the investigator's clinic, you are expected to maintain the established study drug dosing schedule, while continuing to take your methotrexate (MTX) weekly (in the morning or the evening). Study drug can be taken with or without food.

You are being asked to keep a record of every study drug, MTX and folic acid (or equivalent) dose taken for the duration of this study. In addition, record the dose of MTX taken.

Please record the time to the nearest minute. If for any reason a full dose was not taken, please enter in the comments field the details why a full dose was not taken. Please record any missed doses.

Please return your dosing diary with used and unused containers at each clinic visit.

If you have any questions or concerns at any time, please contact your study doctor.

Study Day	Date	Study Drug		MTX		Folic Acid		Comments
		AM Dose	PM Dose	Dose Once Weekly	Time Taken	Daily Dose	Time Taken	
		Time of Dose	Time of Dose					
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								
24								

Appendix L. Latent TB Risk Factor Questionnaire Example

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

From: http://www.mayoclinic.com/health/tuberculosis/DS00372/DSECTION=risk-factors

http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix M. Rheumatology Common Toxicity Criteria v.2.0 Example

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

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

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

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

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

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

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

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

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

I. Neuropsychiatric				
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 O2	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 O2 relieves	Symptomatic at rest, debilitating, requires constant nasal O2
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 O2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity – DLCO)	76% – 90% of pre-treatment value	51% – 75% of pre-treatment value	26% – 50% of pre-treatment value	≤ 25% of pre-treatment value

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

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

OTC = over-the-counter medication; ADL = activities of daily living; IV = intravenous; ECG = electrocardiogram; CHF = congestive heart failure; MRI = magnetic resonance imaging; Hb = haemglobin; LLN = lower limit of normal; ULN = upper limit of normal; WBC = white blood cells; SLE = systemic lupus erythematosus; ANA = antinuclear antibodies; H-2 blockers = histamine-2 blockers; FVC = forced vital capacity

* For CPK and Creatinine NCI CTC grading will be used. For CPK 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

Appendix N. Local Requirements

United Kingdom

Section 1.2 Synopsis and Section 5.2.2 Exclusion Criteria

4. Laboratory values from the visit immediately prior to Baseline Visit meeting the toxicity management criteria (Section 6.10) for abnormal laboratory values requiring study drug interruption/discontinuation.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1,000/µL, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
Absolute lymphocytes counts	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total white blood cell count	• If confirmed < 2,500/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its Baseline value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its Baseline value.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	• Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5. o A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • Interrupt study drug immediately if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF. • For Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within one week: o ALT > 5 × ULN OR o ALT or AST > 3 × ULN if an alternative cause is not readily identified. o A positive result for HBV DNA PCR testing in these subjects will require immediate interruption of study drug and a hepatologist consultation should occur within one week for recommendation regarding subsequent treatment. For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × baseline value and ≤ ULN • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.
Creatine Phosphokinase	• If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie Therapeutic Area Medical Director. For the above CPK elevation scenarios, complete supplemental CPK eCRF.

Appendix O. Prevnar 13® Vaccine Sub-Study

This section describes the requirements, procedures and statistical analyses specific to this sub-study.

16.0 Objective

The objective of this sub-study is to assess the impact of upadacitinib treatment (15 mg QD and 30 mg QD) with background MTX on immunological responses to Prevnar 13® in RA patients.

16.1 Overall Sub-Study Design and Plan: Description

This sub-study will evaluate humoral immune response following Prevnar 13® administration in RA subjects enrolled in the main Study M13-538 treated with either upadacitinib 15 mg QD or 30 mg QD on a stable dose of background MTX. Immune response will be measured at three timepoints (pre-vaccination, 4 weeks post-vaccination, and 12 weeks post-vaccination). Enrollment will continue until approximately 150 subjects have been recruited to participate.

Subjects must be on a stable dose of:

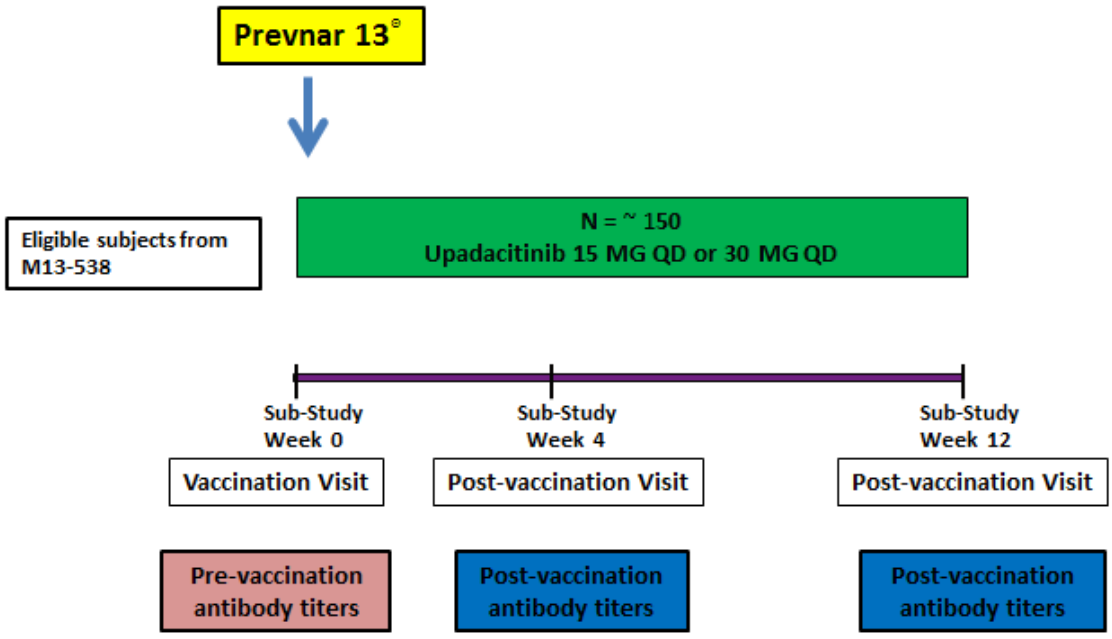
- upadacitinib (15 mg QD or 30 mg QD as assigned in the main study) for a minimum of 4 weeks prior to the Vaccination visit and for at least 4 weeks afterwards.
- background methotrexate for a minimum of 4 weeks prior to the Vaccination visit and for at least 4 weeks afterwards.

The subject's background anti-rheumatic medications (oral or parenteral corticosteroids, if applicable) should also remain stable for a minimum of 4 weeks after the Vaccination visit.

At the Vaccination visit, subjects who have provided a written informed consent for the sub-study will be assessed for eligibility. If eligible, blood samples for the measurement

of pre-vaccination antibody titers will be collected, followed by administration of Prevnar 13® as per the local label prescribing requirements. The criteria and procedures of the main study must still be adhered to in addition to those for the sub-study.

Design Schematic



16.2 Selection of Vaccine Sub-Study Population

A subject may be enrolled in this sub-study provided that he/she has met all of the inclusion criteria specified in Section 16.2.1 and none of the exclusion criteria specified in Section 16.2.2.

16.2.1 Inclusion Criteria

1. Must currently be enrolled in the main study.

2. Must have been receiving a stable dose of upadacitinib (either 15 mg QD or 30 mg QD) for a minimum of 4 weeks prior to the Vaccination visit.
3. Must have been on a stable dose of background methotrexate (no change in dose or frequency) for a minimum of 4 weeks prior to the Vaccination visit.
4. If subject is on corticosteroids, must remain on a stable dose of ≤ 10 mg/day of prednisone or equivalent corticosteroid therapy for at least 4 weeks after the Vaccination visit.
5. Must meet the prescribing specifications as per local label requirements to receive Prevnar 13® vaccine.
6. Willing to receive Prevnar 13® vaccine.

16.2.2 Exclusion Criteria

1. Receiving any csDMARDs other than MTX.
2. Receiving > 10 mg/day of prednisone or equivalent corticosteroid therapy.
3. Receipt of any steroid injection within 4 weeks prior to Vaccination visit.
4. History of severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13®.
5. History of any documented pneumococcal infection within the last 6 months prior to the Vaccination visit.
6. Receipt of any vaccine 4 weeks prior to the Vaccination visit and/or anticipation of any vaccination for 4 weeks after the Vaccination visit.
7. Receipt of any pneumococcal vaccine.
8. Subject is not suitable for the sub-study as per the Investigator's judgment.

16.2.3 Prohibited Therapy

Subjects enrolled into this sub-study will continue on their assigned doses of upadacitinib for at least 4 weeks after the Vaccination visit. Upadacitinib dose may be decreased per Investigator's judgment if there are safety and/or tolerability concerns due to an adverse event or reaching one of the protocol-specific toxicity management thresholds. Subjects will be required to continue on stable doses of background MTX until after the Sub-Study Week 4 visit (4 weeks post-vaccination). Any dosage adjustment and/or initiation of oral or parenteral corticosteroids, or csDMARDs is prohibited until after the Sub-Study Week 4 visit. Adjustment and/or initiation of background anti-rheumatic medications will be allowed at any time after the collection of the Sub-Study Week 4 post-vaccination titer sample.

16.2.4 Efficacy and Safety Assessments/Variables

The study will include a Vaccination visit, followed by a visit 4 weeks post-vaccination for the short-term assessment of immunological responses to Prevnar-13®, and a visit 12 weeks post-vaccination visit for the long-term assessment of immunological responses to Prevnar-13®.

Vaccination Visit

The Vaccination visit (Sub-study Week 0) should occur during any scheduled main study visit. At this visit, subjects will be reviewed against the sub-study inclusion and exclusion criteria (Refer to Section 16.2.1 and Section 16.2.2). Activities for the sub-study should occur only after all procedures for the main study visit have been completed, with the vaccination occurring at the very end of sub-study visit. Subjects enrolled into this sub-study will have a blood draw for the assessment of pre-vaccination antibodies levels specific to Prevnar-13®. Afterwards, subjects will be administered Prevnar-13® as per the local label requirements. The vaccination should occur at the end of the Vaccination visit after all other procedures, including procedures from main study visit, are completed.

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

Post-Vaccination Visits

Subjects should return to the site for 4 week and 12 week post-vaccination visits (Sub-study Week 4 and Sub-Study Week 12) to complete the sub-study procedures identified in Table 6. The 12 week post-vaccination visit should coincide with the subject's regularly scheduled main study visit. At the 4-week post-vaccination visit, blood will be drawn for the assessment of humoral immune responses to Prevnar-13® and assessment of adverse events will be performed. At the 12-week post-vaccination visit, in addition to the main study procedures, collection of blood samples to measure immune response to Prevnar-13® will occur.

Table 6. Sub-Study Activities

Activity	Vaccination Visit[a] (Sub-Study Week 0)	4-Week Post Vaccination Visit (Sub-Study Week 4)	12-Week Post Vaccination Visit (Sub-Study Week 12)
Informed Consent[b]	X		
Inclusion/Exclusion review	X		
Pre-vaccination blood sample collection	X		
Prevnar-13® vaccination	X		
Post-vaccination blood sample collection		X	X
Adverse event assessment[c]		X	

a. The Vaccination and 12 week post-vaccination visits should coincide with the regularly scheduled visits of the main study.

b. The subject must provide consent specific to the sub-study before any related procedures are performed. If the subject does not consent to participate in the sub-study, it will not impact the subject's participation in the main study.

c. Collection and assessment of AEs will be completed as outlined in the main study.

16.2.5 Statistical Analysis of Efficacy

Primary Variables

1. Proportion of subjects with satisfactory humoral response to Prevnar 13® at the Week 4 visit of the sub-study (4 weeks post-vaccination).

Satisfactory humoral response to Prevnar 13® is defined as greater than or equal to (≥) 2-fold increase in antibody concentration from the vaccination baseline in at least 6 out of the 12 pneumococcal antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).

Secondary Variables

1. Proportion of subjects with satisfactory humoral response to Prevnar 13® at the Week 12 visit of the sub-study (12 weeks post-vaccination).
2. Geometric Mean Fold Rise (GMFR) of anti-pneumococcal antibody levels to each of the 12 pneumococcal antigens above vaccination baseline values at Week 4 and Week 12 of the sub-study

16.2.6 Statistical Methods and Determination of Sample Size

Statistical and Analytical Plans

All efficacy analyses will be carried out using the Full Analysis Set population of the Vaccine Sub-study, which includes all enrolled subjects who were vaccinated and received at least one dose of study drug after vaccination during the sub-study. Subjects will be classified into upadacitinib 15 mg QD dose group or upadacitinib 30 mg QD dose group based on their upadacitinib dose at the vaccination visit.

The proportion of subjects achieving Satisfactory Humoral Response will be summarized by count and percentages for each upadacitinib dose group at 4 weeks post-vaccination

and 12 weeks post-vaccination. 95% confidence intervals for each upadacitinib dose group will be provided.

At 4 weeks post-vaccination and 12 weeks post-vaccination, the geometric mean fold rise (GMFR) and corresponding 95% confidence intervals of anti-pneumococcal antibodies as compared with pre-vaccination will be summarized for each upadacitinib dose group. Calculations will be done using logarithmically transformed assay results, and then back-transformed to the original scale.

All efficacy analyses will be based on observed cases. No multiplicity adjustment is planned for any analysis in this vaccine sub-study.

Determination of Sample Size

A total sample size of approximately 150 subjects is planned for the sub-study, where approximately 100 subjects are expected to be on upadacitinib 15 mg QD dose. Assuming a satisfactory humoral response rate of 60%, the planned sample size of approximately 100 subjects for upadacitinib 15 mg QD group will provide a margin of error of approximately 10% for this dose group when using a 95% confidence interval.