

1.0 Title Page

Clinical Study Protocol M14-500

A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected via Imaging TEchniques, Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA)

Incorporating Administrative Changes 1, 2 and 3, and Amendment 1

AbbVie Investigational Product:	Adalimumab	
Date:	25 February 2016	
Development Phase:	4	
Study Design:	A Phase 4, multicenter, randomized, double-blind parallel-group study: dose tapering of adalimumab controlled by withdrawal, in subjects with rheumatoid arthritis in stable clinical remission	
EudraCT Number:	2014-001114-26	
Investigators:	Investigator information is on file at AbbVie	
Sponsor:	For Non-EU Countries: AbbVie 1 North Waukegan Road [REDACTED] North Chicago, IL 60064	For EU Countries: AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany
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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.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	15 May 2014
Administrative Change 1	15 July 2014
Administrative Change 2	10 March 2015
Administrative Change 3	21 May 2015

The purpose of this amendment is to:

- Throughout protocol: Reduce sample size population from 334 to approximately 200 enrolled subjects.

Rationale: *The sample size was evaluated to ensure a certain level of precision for the estimation of the correlation coefficient between Baseline magnetic resonance imaging (MRI) score and the occurrence of flare. Recently published data have shown overall a high rate of flare/relapse/treatment failure and that sub-clinical synovitis might be a predictor of flare upon biological disease-modifying anti-rheumatic drug (bDMARD) withdrawal. Based on the review of these data, a sample size of 150 in the dose tapering arm has been recalculated to meet the study objectives.*

- Section 1.2, Synopsis, Section 3.3.1, Additional Considerations on Key Study Parameters, Section 5.1, Overall Study Design and Plan: Description, Section 5.2.1, Inclusion Criteria, Inclusion Criterion 4, Section 5.2.2, Exclusion Criteria, Exclusion Criterion 1, Section 5.3.1.1, Study Procedures, allow for 3 variables of the Disease Activity Score DAS28 (c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) to satisfy inclusion criteria purposes of patients in stable remission defined as DAS28 < 2.6 for ≥ 6 months and exclusion criteria of patients with DAS28 (CRP or ESR) ≥ 2.6 within 6 months prior to Screening.

Rationale: *To align with clinical practice and other clinical studies when the Patient Global Assessment (PGA) is not routinely documented and because the DAS28 with three variables is validated.*

- Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan:
Description: Inclusion Criteria 3, 5, 6 and 7, change period of time for required stable medications (e.g., methotrexate (MTX) stable dose for ≥ 12 weeks; other DMARDS at stable dose for ≥ 12 weeks and steroids/NSAIDs stable for ≥ 4 weeks) up to Week 0 instead of up to Screening.
Rationale: *As per previous studies and treatment effect of csDMARDs, a period of stable medication prior to inclusion (and not screening) is enough to ensure medication which could affect risk of flare is stable.*
- Section 1.2, Synopsis, Section 3.3.1, Additional Considerations on Key Study Parameters, Section 5.2.3.1, Prior Therapy, Section 5.6.3, Suitability of Subject Population, Inclusion Criterion 3, allow for up to 20% of subjects to be included in the study if on stable other csDMARDs and/or on monotherapy adalimumab (no csDMARDs) for at least 12 weeks prior to Week 0. Once the limit of 20% of enrolled subjects on other csDMARDs or no csDMARDs is met, only subjects on concomitant methotrexate will be allowed into the trial.
Rationale: *To align with clinical routine practice as shown in several registries and other real world evidence in which around 30% – 34% of patients are not taking concomitant MTX with a bDMARD and still include the majority of patients treated with concomitant stable MTX. The primary analysis of association between baseline MRI and flare remain unchanged. Concomitant use of treatment will be examined in the sensitivity analysis to account for potential differential effect.*
- Section 1.2, Synopsis, clarify language regarding MRI scans.
Rationale: *To clarify that if both hands/wrists are affected then the dominant hand and wrist should be scanned.*
- Section 1.2, Synopsis and Section 5.2.3.2, Concomitant Therapy, Inclusion Criterion 3, add that intra-muscular methotrexate is allowed as a concomitant therapy.
Rationale: *To align with current methotrexate therapies.*
- Section 1.2, Synopsis, increase potential number of sites and countries where the study will be conducted.

Rationale: *To accurately reflect the number of sites and countries that are planned to ensure timely enrollment of the study.*

- Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan: Description, Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, extend screening period to up to 28 days (instead of 21); screening may be exceptionally extended upon justification and further consultation with the Study Designated Physician.

Rationale: *To allow enough time for screening procedures and to align the Week 0 visit with the pre-scheduled adalimumab injection.*

- Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan: Description:, allow for an extension of the Lead-in Period to up to 6 weeks (instead of 4 weeks) if required to provide enough time for Lead-in procedures.

Rationale: *To align the Week 4 visit with the next pre-scheduled adalimumab injection and to provide adequate time for study procedures during the lead-in period (namely MRI) prior to Baseline Week 4 Visit.*

- Section 1.2, Synopsis, Inclusion Criterion 7, include the use of tramadol or other equivalent opioids and/or non-opioid analgesics to be at a stable dose and/or therapeutic scheme for at least 4 weeks prior to the Week 0 visit.

Rationale: *To allow for other equivalent opioids to Tramadol available in some countries to be used.*

- Section 5.1, Overall Study Design and Plan: Description, add further clarification on the importance of stopping commercial adalimumab when the subject enrolls in the study.

Rationale: *To ensure subjects are not taking commercial adalimumab during the study.*

- Section 5.1, Overall Study Design and Plan: Description, increase the dosing window during the double-blind period to ± 3 days.

Rationale: *To allow for flexibility of scheduling within a period which does not affect treatment efficacy and allows for adjustment of the visit scheduling accommodating weekends.*

- Section 5.1, Overall Study Design and Plan: Description, allow for a local MRI report to be viewed for safety reasons on findings not related to rheumatoid arthritis.
Rationale: *To ensure the safety of the subject.*
- Section 5.1, Overall Study Design and Plan: Description, clarify that during the Open-Label Rescue Arm csDMARDs including MTX (initiation and/or dose or administration mode change) are included. Excluded csDMARDs that are not allowed include azathioprine, cyclophosphamide and d-penicilamine.
Rationale: *To ensure the safety of the subject while on rescue therapy.*
- Section 5.1, Overall Study Design and Plan: Description, Table 1, Study Activities, table note "d.," add an option for a shortened Early Termination Visit for those subjects terminating the study in the Lead-in period from Week 0 up to Week 4.
Rationale: *To allow for a shortened version of the Early Termination Visit (reasons for discontinuation, review of adverse events and Investigational Product and Diary return) for those subjects on open-label adalimumab who have not yet been randomized since these subjects have not changed any of their previous treatment and will not be analyzed for the primary or secondary objectives.*
- Section 5.1, Overall Study Design and Plan: Description, add that all subjects who discontinue the study will have a follow-up phone call approximately 70 days after the last administration of study drug.
Rationale: *To obtain information on any new or ongoing adverse events for all subjects.*
- Revised timing of first dose of Open-Label Rescue arm at the Flare Unscheduled Visit in Section 5.1, Overall Study Design and Plan: Description.
Rationale: *To allow for an immediate start of the Open-Label Rescue Arm (at least 1 day after last dose).*
- Add "A CXR may be required for evaluation of active TB" in Table 1, Study Activities, table note "g.," Section 5.1, Overall Study Design and Plan: Description.

Rationale: *To reinforce that a CXR may be required to evaluate active TB.*

- Section 5.2.2, Exclusion Criteria, remove azathioprine from exclusion criteria to allow for patients who have been previously, but are not currently, treated with azathioprine and who have no other severe diseases to be included.

Rationale: *Patients who are in clinical remission for at least 6 months and on treatment with adalimumab for at least 1 year are not expected to develop any prior azathioprine exposure related complications as per absence of evidence in a literature review.*

- Section 5.2.3.1, Prior Therapy, Section 5.2.3.2, Concomitant Therapy, allow for a decrease in the dose of methotrexate or other csDMARDs during the 12 weeks prior to Week 0 and throughout the study.

Rationale: *To allow for a dose decrease in the case of an event of intolerability (or other safety issues) related to methotrexate or other csDMARDs.*

- Section 5.2.3.1, Prior Therapy, allow for an interruption of up to two non-consecutive doses of adalimumab within the past 12 months but not during the 12 weeks prior to Week 0 if due to a non-RA related event (e.g., infection, surgery).

Rationale: *To align with clinical practice and product interruptions due to, for example, an infection as also described in prescribing information.*

- Section 5.2.3.2, Concomitant Therapy, add that subjects should take a dietary supplement of oral folic acid 5 mg once weekly "or per local guidelines per the investigator's discretion" if taking concomitant MTX.

Rationale: *To allow for folic acid dosage to conform with current clinical practice per local guidelines.*

- Correct timing of urine pregnancy test collection from the Baseline visit to Week 0 in Table 1, Study Activities, table note "1," Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, and also in Section 5.3.1.1, Study Procedures.

Rationale: *To correct an inadvertent error. Urine pregnancy test is due at the Week 0 visit and not Baseline visit per Exclusion Criterion 21.*

- Revise text in Table 1, Study Activities, table note "l." in Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, to state that urine pregnancy samples will be performed locally.

Rationale: *To correct in advertent error in the protocol and to make consistent with Section 5.3.1.1.*

- Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, remove table note "d." from Table 1, Study Activities. Study Activities regarding using the ESR at Screening for assessment at Day 1.

Rationale: *To avoid confusion since the ESR taken at each visit should be used to calculate the DAS 28 (ESR) on the day of the current visit.*

- Section 5.3.1.1, Study Procedures, add that the 3 variable DAS28 (ESR) score can be used to evaluate flare during the trial when the PGA score is not available upon discussion with the Study Designated Physician.

Rationale: *To allow for evaluation of the flare when the PGA score is not available through the electronic reported outcome devices.*

- Clarify in Section 5.3.1.1, Study Procedures, that the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) will be calculated as part of the statistical analysis. Calculation is not required by the site.

Rationale: *To clarify that calculation is not required by the site.*

- Remove in Table 1, Study Activities, the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI).

Rationale: *To clarify that calculation is not required by the site.*

- Revise the measurement unit of ESR in Section 5.3.1.1, Study Procedures, from mm/Hg to the correct unit mm/Hr.

Rationale: *To correct a typographical error.*

- Remove the word "locally" referring to performance of TB Screening in Section 5.3.1.1, Study Procedures.

Rationale: *To conform to the protocol where TB screening could be done centrally or locally.*

- Revise language to the duration of treatment in Section 5.5.1, Treatments Administered.

Rationale: *In order to maintain consistent wording throughout the protocol.*

- Add the Complaint and Product Complaint definition to Section 6.0, Complaints, Section 6.2.1, Definition and Section 6.2.2, Reporting as well as the reporting requirements for Product Complaints.

Rationale: *To comply with current AbbVie standards.*

- Add 24-hour medical surveillance contact information in Section 6.1.5, Adverse Event Reporting.

Rationale: *To update protocol with AbbVie's standard 24-hour medical surveillance information in case the Study Designated Physician is unavailable.*

- Add information regarding the Electronic Patient Reported Outcomes (ePROs) in Section 10.3, Electronic Patient Reported Outcomes (ePROs).

Rationale: *To provide additional information on how data is collected and reviewed.*

- Revise Injection Instructions in Appendix C, Injection Instructions – Pre-Filled Syringe – Sample.

Rationale: *To correct an error in how many syringes the subject will take home at one time.*

- Remove tuberculosis language specific to the Czech Republic.

Rationale: *The Czech Republic is not participating in the trial.*

- Appendix K, Short Form-36 (SF-36) Health Survey Questionnaire – Sample:, update the Short Form-36 (SF-36).

Rationale: *To include the version used for electronic patient reported outcomes.*

- Corrected minor typographical errors throughout the document.

An itemized list of all changes made to this protocol under this amendment can be found in [Appendix P](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M14-500
Name of Study Drug: Adalimumab	Phase of Development: 4
Name of Active Ingredient: Adalimumab	Date of Protocol Synopsis: 25 February 2016
<p>Protocol Title: A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected via Imaging TEchniques Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA)</p>	
<p>Objectives: The primary objective is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects randomized to an adalimumab dose tapering regimen controlled by adalimumab withdrawal. The Secondary Objectives are:</p> <ul style="list-style-type: none"> • To assess the occurrence and severity of flares and the time to flare in both taper and withdrawal arms. • To investigate the association between Double-Blind Baseline (dbBaseline) subject demographic and disease characteristics and the occurrence of flares. • To investigate the association between dbBaseline adalimumab trough concentrations and the occurrence of flares. • To evaluate the effectiveness of rescue therapy with open-label adalimumab 40 mg every other week (eow) over 16 weeks in subjects experiencing a flare. • To assess the change in rheumatoid arthritis MRI scoring system (RAMRIS) scores from Baseline to Final visit in the taper, withdrawal and Open-Label Rescue Arms. • To investigate the MRI-flare associations in sub-groups of subjects who meet additional clinical remission criteria at dbBaseline including simplified disease activity index (SDAI) ≤ 3.3, clinical diseases activity index (CDAI) ≤ 2.8 and ACR/EULAR 2011 boolean-based remission, as well as to describe the course of disease and patient reported outcome (PRO) measures in the taper, withdrawal and Open-Label Rescue Arms overall and per dbBaseline subgroup. • To assess the rate of anti-adalimumab antibodies (AAA) positive subjects in the taper and withdrawal arms. <p>The study also has the following exploratory objectives:</p> <ul style="list-style-type: none"> • In the subgroup of subjects with a Baseline Ultrasound (US) assessment: <ul style="list-style-type: none"> ○ To investigate the association between Baseline ultrasound scores and the occurrence of flares. ○ To investigate the association between the Baseline ultrasound scores and Baseline MRI RAMRIS scores. ○ To describe the change in the ultrasound scores from Baseline to the time of the occurrence of a flare in the taper and withdrawal arms. • To investigate the association between biomarker values at dbBaseline (and their change over time) and the occurrence of flares. 	

<p>Investigators: Investigator information is on file at AbbVie.</p>
<p>Study Sites: Approximately 72 sites in North America, Europe and Australia</p>
<p>Study Population: Subjects age ≥ 18 years diagnosed with RA, on a stable dose of adalimumab 40 mg subcutaneously (sc) eow (for ≥ 12 months prior to Week 0 Visit) in combination with methotrexate (MTX) (at stable dose for ≥ 12 weeks prior to Week 0 Visit) or if not on MTX, another allowed conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) at stable dose or no csDMARDs for ≥ 12 weeks prior to Week 0 Visit) and in documented clinical remission, defined as DAS28 erythrocyte sedimentation rate (ESR) < 2.6 or DAS28 c-reactive protein (CRP) < 2.6, for ≥ 6 months prior to the Screening Visit and DAS28 (ESR) < 2.6 at the Screening Visit. Patients who are not treated with concomitant stable dose of MTX are limited to a maximum of 20% of the study population.</p>
<p>Number of Subjects to be Enrolled: Approximately 200</p>
<p>Methodology: This is a Phase 4, multicenter, randomized, double-blind, parallel-group study in subjects with RA who are in stable clinical remission defined as DAS28 (ESR) or DAS28 (CRP) < 2.6 for at least 6 months prior to the Screening Visit. Though the cut-off for clinical remission of DAS28 (CRP) may not be equivalent to the DAS (ESR), in clinical practice both are frequently used to define remission as < 2.6. Both ESR or CRP and 4 or 3 (when Patient Global Assessment [PGA] is not available) variables DAS28 will be allowed for the purposes of identifying subjects for Screening; however, throughout the study clinical remission will be defined by the more stringent 4 variables DAS28 (ESR) < 2.6 criteria. At Screening, only subjects with confirmed 4 variables DAS28 (ESR) < 2.6 will be considered for inclusion in the study. The study activities will start with a Screening Period of up to 28 days to confirm inclusion/exclusion criteria including a DAS28 (ESR) assessment of < 2.6. Subjects who have signed the Informed Consent and who fulfill all Screening criteria will enter the study. The study starts with a 4-week Lead-In Open-Label (OL) Period during which stable DAS28 (ESR) clinical remission in 2 assessments 4 weeks apart will be confirmed. Subjects will receive adalimumab 40 mg sc eow starting at the Week 0 Visit of the Lead-In Period; this will be approximately 2 weeks after their last commercial Humira[®]. If needed for study procedures completion or injection scheduling adjustment, the lead-in period can be extended for up to 2 more weeks in which case the Week 4 Visit study procedures will occur up to 6 weeks after the Week 0 Visit. At Week 4, the end of the Lead-In Period, subjects will have a dbBaseline visit. Subjects must have a confirmed DAS28 (ESR) remission at two time points in order to be randomized: 1. DAS28 (ESR) < 2.6 at the Lead-In Period Week 0 2. DAS28 (ESR) < 2.6 at the dbBaseline visit Week 4 Subjects who meet the remission criteria will be randomized (5:1) to one of two double-blind arms and followed for additional 36 weeks in the Double-Blind Period: 1. A reduced frequency of adalimumab 40 mg sc every 3 weeks (q3wks): taper arm, or 2. Adalimumab placebo sc q3wks: withdrawal arm.</p>

Methodology (Continued):

All subjects who are taking concomitant MTX (any dose oral, subcutaneous [sc] or intramuscular [im]) and/or other csDMARDs at a stable dose for at least 12 weeks prior to Week 0 Visit will maintain the regimen throughout the Lead-In and Double-Blind Periods of study. Subjects who have not been taking any csDMARDs for at least 12 weeks prior to the Week 0 Visit, will also maintain this regimen throughout the Lead-In and Double-Blind Periods of study.

Any other allowed RA concomitant medications should also be kept stable throughout the Lead-In and Double-Blind Periods of the study; these medications and MTX will be received by local prescriptions.

During the Double-Blind Period, subjects will be evaluated every 6 weeks for efficacy, including detection of flares, PROs, safety and laboratory assessments at scheduled visits on: Weeks 4, 10, 16, 22, 28, 34 and 40 (Final visit).

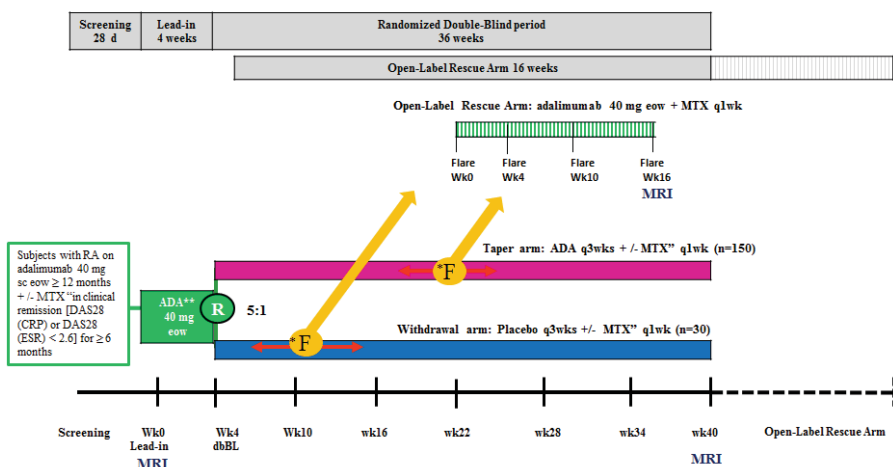
Other unscheduled visits will occur in the suspected event of a flare. During the interval between scheduled visits, subjects will be asked to contact their physicians in case of feeling their disease is worsening: an unscheduled visit will be performed within 2 weeks of contact with the site to assess if subjects are experiencing a flare.

Subjects with a confirmed flare (defined as an increase from dbBaseline in DAS28 [ESR] of > 0.6 AND a DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR]) at any time point (at a scheduled or unscheduled visit) will undergo Flare Week 0 visit procedures and will be immediately switched to an Open-label rescue arm initiating adalimumab 40 mg eow rescue therapy.

In the Open-Label Rescue Arm, subjects will be further evaluated at Flare Weeks 4, 10 and 16 for efficacy, PROs, safety and laboratory assessments.

During this period, further treatment escalation/change will be allowed based on the Investigator's medical judgment. Any treatments escalation/change will be documented. At Flare Week 0, all subjects will be requested to initiate weekly at home self-assessment of their RA disease activity by using Routine Assessment of Patient Index Data (RAPID)-3 questionnaires until Week 16.

See study schematic below:



* Flare at any time point; Flare defined as: DAS28 (ESR) ≥ 2.6 AND an increase in DAS by > 0.6 OR an increase in DAS28 (ESR) by ≥ 1.2 from dbBaseline irrespective of DAS28(ESR); Subjects who flare at any time during the randomized Double-Blind period will be switched to OL ADA 40 mg eow and continue in the Open-Label Rescue Arm for 16 weeks up to a maximum study duration of 36 weeks.
** ADA = adalimumab
*** at least 80 % of patients in combination treatment with stable MTX ≥ 12 weeks; up to 20% on stable other csDMARDs or adalimumab monotherapy ≥ 12 weeks

Methodology (Continued):

A high-field contrast MRI of the most affected hand (2nd to 5th MCP) and wrist will be performed on all subjects during the Lead-In Period (prior to the dbBaseline visit) and at Final/Early Termination Visit. If both sides are considered equally affected, the MRI of the dominant hand (2nd to 5th MCP) and wrist will be performed.

The acquired MRI images will be centrally read and Investigators will be blinded to the results. Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.

In sites that meet pre-specified ultrasound requirements and who wish to participate in the ultrasound portion of the study, subjects will undergo US assessment using Gray Scale Ultrasonography (GSUS) and Power Doppler Ultrasonography (PDUS) consisting of a systematic longitudinal and transverse multiplanar examination of 46 joints and 18 tendon/tendon compartment during Lead-In or at dbBaseline Visit prior to randomization and at the Flare Week 0 Visit (if applicable). US will be performed and assessed by local Ultrasonographer independent of the clinical assessor who will be blinded to the US scores.

Pharmacokinetics (PK) and immunogenicity will be assessed based on serum adalimumab trough concentrations and serum anti-adalimumab antibodies (AAA), respectively. Blood samples for adalimumab concentrations and measurements of AAA will be taken prior to dosing at dbBaseline (Week 4), at Weeks 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable).

A panel of inflammatory biomarkers: matrix metalloproteinase 3 (MMP3), Collagen neo-epitope (C1M), Type III collagen neo-epitope (C3M), Matrix metalloproteinase-mediated c-reactive protein (CRPM), Matrix metalloproteinase-degraded citrullinated vimentin (VICM), Serum amyloid-associated protein (SAA), Interleucin-6 (IL-6), Chemokine (C-X-C motif) ligand 10 CXCL10 and CXCL13 will be assessed at dbBaseline (Week 4), Weeks 10, 16, 28, 40 or at Early Termination, Flare Weeks 0, 4 and 16 (if applicable) on blood samples taken prior to dosing. At the time of analysis, other potential biomarkers identified as adding value to predict flare in this patient population may be included.

Additional optional samples for future biomarker research will be collected.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- Male or female subjects \geq 18 years of age.
- Subject has a diagnosis of RA as defined by the 1987 revised ACR classification criteria and/or the ACR/EULAR 2010 classification criteria (any duration since diagnosis).
- Subject must meet the following criteria:
 - Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Week 0 Visit;
 - Must be treated with concomitant MTX at a stable dose (oral, sc or im at any dose) for at least 12 weeks prior to Week 0 Visit or if not on MTX, must be treated with other allowed csDMARDs at stable dose for at least 12 weeks prior to Week 0 Visit or if not treated with csDMARDs must maintain this regimen for at least 12 weeks prior to Week 0 Visit.
- Subject must be in sustained clinical remission based on the following:
 - At least one documented 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) $<$ 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
 - 4 variables DAS28 (ESR) assessed at Screening $<$ 2.6, with all components including ESR assessed at Screening.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- If subjects are receiving concomitant allowed csDMARDs (in addition or not to MTX) the dose must be stable for at least 12 weeks prior to the Week 0 Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
- If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to the Week 0 Visit.
- If subjects are receiving concomitant non-steroidal anti-inflammatory drugs (NSAIDs), tramadol or other equivalent opioids and/or non-opioid analgesics, the dose and/or therapeutic scheme must be stable for at least 4 weeks prior to the Week 0 Visit.
- Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Main Exclusion:

- Any 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit ≥ 2.6 .
- Subject is on an additional concomitant biological disease-modifying anti-rheumatic drug (bDMARD) (including but not limited to abatacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab or tocilizumab).
- Subject has been treated with intra-articular or parenteral corticosteroids within the last 4 weeks before Screening.
- Subject has undergone joint surgery within 12 weeks of Screening (at joints to be assessed by MRI and/or ultrasound).
- Subject has a medical condition precluding an MRI (e.g., magnetic activated implanted devices – cardiac pace-maker, insulin pump, neurostimulators, etc. and metallic devices or fragments or clips in the eye, brain or spinal canal and in the hand/wrist undergoing MRI).
- Subject has a medical condition precluding a contrast MRI with gadolinium (e.g., nephrogenic systemic fibrosis, previous anaphylactic/anaphylactoid reaction to gadolinium containing contrast agent, pregnancy or breastfeeding, severe renal insufficiency with an estimated Glomerular Filtration Rate [eGFR] below 30 mL/min/1.73 m² at Screening, hepato-renal syndrome, severe chronic liver function impairment).
- Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Screening Visit.

Investigational Product:	Adalimumab
Dose:	Lead-In Period: Adalimumab 40 mg OL eow for 4 weeks Double-Blind Period: Adalimumab 40 mg q3wks for 36 weeks Open-Label Rescue Arm: Adalimumab 40 mg OL eow for a minimum of 16 weeks
Mode of Administration:	Subcutaneously (SC) pre-filled syringe

Reference Therapy:	Placebo for the Double-Blind Period
Dose:	0.8 ml q3wks
Mode of Administration:	Subcutaneously (SC) pre-filled syringe
Duration of Treatment:	<p>The duration of treatment will include a 4-week Lead-In Period (adalimumab 40 mg sc eow) followed by a 36-week, randomized, Double-Blind Period with 2 arms: taper arm (adalimumab 40 mg sc q3wks) controlled by withdrawal matching placebo arm. Open-Label Rescue Arm (adalimumab 40 mg sc eow) will be provided for 16 weeks (if applicable). Therefore, the total duration of the study is 40 or 56 weeks (if applicable).</p>
Criteria for Evaluation:	<p>Efficacy:</p> <p>Primary Efficacy Variables</p> <ul style="list-style-type: none"> The primary explanatory variables are the Baseline hand and wrist synovitis and bone marrow edema (BME) RAMRIS scores as well as a composite of both and the dependent variable is the occurrence of flare up to Week 40 in the tapering arm. <p>Secondary Variables</p> <ul style="list-style-type: none"> Time to flare Flare severity Proportion of subjects experiencing a flare Subject demographics and clinical disease characteristics at dbBaseline, including <ul style="list-style-type: none"> Smoking status, co-morbidities, anti-citrullinated peptide antibody (ACPA) status, Rheumatoid Factor (RF) status, disease duration, previous treatment with conventional synthetic Disease Modifying Anti-rheumatic Drugs (csDMARDs) or biologic Disease Modifying Anti-rheumatic Drugs (bDMARDs) or both, duration of adalimumab therapy, remission duration, disease activity, c-reactive protein (CRP) and Health Assessment Questionnaire (HAQ) score Proportion of subjects who regain clinical remission (defined as DAS28 [ESR] < 2.6 and defined as DAS28 (ESR) decrease > 1.2 if DAS28 [ESR] was less than 2.6 at flare) in the Open-Label Rescue Arm over time Time to regain clinical remission in the Open-Label Rescue Arm Proportion of subjects with low disease activity (defined as DAS28 [ESR] < 3.2) in the Open-Label Rescue Arm over time Change from Baseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI: DAS28 [ESR] < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8) throughout the study Change from dbBaseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores Change from Baseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI: DAS28 [ESR] < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8) throughout the study

Criteria for Evaluation (Continued):

Efficacy (Continued):

Secondary Variables (Continued)

- Change from dbBaseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores
- Change from Baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) over time
- Proportion of subjects with HAQ-DI normal (HAQ-DI \leq 0.5) at dbBaseline and at Week 40
- Change from dbBaseline in RAPID 3 scores assessed during Visits
- Change from Flare Week 0 in RAPID 3 at home assessments
- Change from dbBaseline in Swollen Joint Count (both 28 and 66 joints)
- Change from dbBaseline in Tender joint Count (both 28 and 68 joints)
- Change from dbBaseline in Patient's Global Assessment of Disease activity
- Change from dbBaseline in Patient's Global Assessment of RA pain
- Change from dbBaseline in Physician's Global Assessment of Disease activity
- Change from dbBaseline in morning stiffness assessment
- Change from dbBaseline in Sleep disturbance assessment
- Change from dbBaseline in Treatment Satisfaction Questionnaire for Medication (TSQM)
- Change from dbBaseline in Work Productivity and Activity Impairment (WPAI)
- Change from dbBaseline in Short Form-36 (SF-36)
- Change from dbBaseline in Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-fatigue)
- Change from dbBaseline in CRP
- Change from dbBaseline in ESR

Exploratory Variables

- Baseline and change from Baseline to the time of flare in PDUS and GSUS individual and composite scores of synovitis, synovial hypertrophy and tenosynovitis
- dbBaseline and change from dbBaseline on biomarker values (MMP3, SAA, C1M, C3M, CRPM, VICM, IL-6, CXCL10, CXCL13)

Pharmacokinetics:

- Adalimumab concentrations measurement dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable)
- AAA measurement at dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4, 10 and 16 (if applicable)

Interim Analysis for Double-Blind Baseline Characteristics:

There are few data describing patient disease characteristics, including markers of residual inflammation (such as sensitive imaging assessments and potential biomarkers) and drug levels in patients who are in sustained RA clinical remission on a stable treatment with a TNFi and MTX and/or with other csDMARDs(s) or in TNFi monotherapy. An interim analysis will be conducted to describe the dbBaseline characteristics of this RA population. It will be performed after the dbBaseline assessments and randomization of the entire study population have been completed.

Criteria for Evaluation (Continued):

Safety:

Screening assessments will include medical history, vital signs, physical examination, and clinical and laboratory tests. The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, physical examination (if required) and laboratory tests.

Statistical Methods:

Efficacy:

Analysis for Primary Objective:

The association between the occurrence of flares and Baseline MRI RAMRIS scores will be examined using logistic regression, which is deemed as the main analysis to address the primary objective. Additional analyses will be performed to assess this association using various statistical methods. Specifically, descriptive statistics of Baseline MRI RAMRIS scores will be provided for the two groups of subjects who flare and who do not flare, and the between-group difference in the mean scores will be computed together with a 90% confidence interval (CI). Linear regression will be used to model the relationship between the DAS28 (ESR) at flaring (or at end of study for subjects who do not flare) and the Baseline MRI RAMRIS scores. Receiver operating characteristic (ROC) curve approach will also be utilized to investigate the potential flare prediction criteria based on MRI RAMRIS scores. All model based analyses may adjust for dbBaseline clinical patient characteristics including disease duration, previous and concomitant treatment, etc. when appropriate.

Similar analysis will be conducted for RAMRIS synovitis scores, BME scores and the composite of both.

Analysis for Secondary Objectives:

Within the analyses to address the secondary objectives the association between dbBaseline disease characteristics and the occurrence of flares will be examined using similar analyses as for the primary objective. In addition, characterization of flares, response to rescue therapy in subjects experiencing a flare and the clinical and patient reported efficacy outcomes for all trial subjects will be analyzed accordingly.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by treatment arm at each time point using descriptive statistics. The association between dbBaseline adalimumab trough concentrations and the occurrence of flares will be assessed. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

AAA will be evaluated for each subject and each study arm, and rates of AAA positive subjects will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment emergent adverse events may be evaluated.

Statistical Methods (Continued):**Safety:**

Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA) 17.0 dictionary, by system organ class and by causality to the study medication as assessed by the Investigator will be provided. Laboratory test values will be summarized over time.

Determination of Sample Size:

The planned total number of subjects enrolled into the Lead-In Period is approximately 200.

To estimate the odds ratio for the occurrence of flare with baseline MRI score based on historical MRI data, an effective sample size of 150 subjects in the dose tapering group will ensure a precision for the estimation with the width of 90% CI no more than 0.03 for an odds ratio 1.03, no more than 0.07 for an odds ratio 1.1, and no more than 0.14 for an odds ratio 1.2. Such sample size will also ensure a precision for the estimation of a correlation coefficient ρ with the width of 90% CI of ρ no more than 0.26 for a mild correlation coefficient 0.28, no more than 0.18 for a moderate correlation coefficient 0.55, and no more than 0.13 for a higher correlation with $\rho = 0.67$. Assuming a 30% flare rate, this sample size will provide the precision that the 2-sided 90% CI of the flare rate has a half width no more than 6%.

Under a 5:1 randomization ratio (dose tapering vs. withdrawal), a total of 180 subjects will be randomized. Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 200 subjects will need to be enrolled into the Lead-In Period.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-adalimumab antibodies
ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
ANA	Antinuclear antibodies
BCG	Bacillus Calmette-Guérin
bDMARD	Biological disease-modifying anti-rheumatic drug
BME	Bone marrow edema
C1M	Collagen neo-epitope
C3M	Type III collagen
CDAI	Clinical Disease Activity Index
CDC	Center for Disease Control
CI	Confidence Interval
CRA	Clinical Research Associate
CRP	c-reactive protein
CRPM	Matrix metalloproteinase-mediated c-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CXCL10	Chemokine (C-X-C motif) ligand 10
CXCL13	Chemokine (C-X-C motif) ligand 13
CXR	Chest X-Ray
DAS	Disease Activity Score
dbBaseline	Double-Blind Baseline
DMARD	Disease-modifying antirheumatic drugs
DNA	Deoxyribonucleic acid
dsDNA	Double stranded deoxyribonucleic acid
ECG	Electro Cardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ew	every other week
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism

FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
GSUS	Gray scale ultrasonography
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotropin
HCP	Health care professional
HIV	Human immunodeficiency virus
HRQoL	Health Related Quality of Life
i.a.	Intra-articular
IEC	Independent Ethics Committee
IgG1	Immunoglobulin
IgM	Immunoglobulin M
IGRA	Interferon-Gamma Release Assay
IL-6	Interleucin-6
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IV	Intravenous
LDA	Low disease activity
ln	Natural logarithm
LT	Liver transportation
MCP	Metacarpophalangeal joint
MedDRA	Medical Dictionary for Regulatory Activities
MMP3	Matrix metalloproteinase 3
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTP	Metatarsophalangeal joint
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OL	Open-label
OMERACT	Outcome Measures in Rheumatology
PA	Posterior-anterior

PDUS	Power Doppler ultrasonography
PG	Pharmacogenetic
PGA	Patient's Global Assessment
PhGA	Physician's Global Assessment
PIP	Proximal Interphalangeal joint
PML	Progressive multifocal leukoencephalopathy
PK	Pharmacokinetics
PPD	Purified protein derivative
PRO	Patient Reported Outcome
q3wks	Every 3 weeks
QoL	Quality of Life
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid arthritis MRI scoring system
RAPID-3	Routine Assessment of Patient Index Data
RF	Rheumatoid factor
ROC	Receiver operating characteristic
SAA	Serum amyloid-associated protein
sc	Subcutaneous
SDAI	Simplified Disease Activity Index
SF-36	Short Form-36
SJC	Swollen Joint Count
STIR	Short tau inversion recovery
TB	Tuberculosis
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor inhibitor
TSQM	Treatment Satisfaction Questionnaire for Medication
US	Ultrasonography
VAS	Visual Analog Scale
VICM	Matrix metalloproteinase-degraded vimentin
WPAI	Work Productivity and Activity Impairment

2.0	Table of Contents	
1.0	Title Page	1
1.1	Protocol Amendment: Summary of Changes	2
1.2	Synopsis	9
1.3	List of Abbreviations and Definition of Terms.....	18
2.0	Table of Contents	21
3.0	Introduction	26
3.1	Disease Overview	26
3.2	Adalimumab Overview	26
3.3	Rationale for the Study	27
3.3.1	Additional Considerations on Key Study Parameters.....	29
3.4	Safety Information	34
3.5	Differences Statement.....	34
3.6	Benefits and Risks.....	35
4.0	Study Objectives	35
5.0	Investigational Plan	37
5.1	Overall Study Design and Plan: Description	37
5.2	Selection of Study Population.....	45
5.2.1	Inclusion Criteria	45
5.2.2	Exclusion Criteria	48
5.2.3	Prior and Concomitant Therapy.....	51
5.2.3.1	Prior Therapy	51
5.2.3.2	Concomitant Therapy.....	53
5.2.3.3	Prohibited Therapy.....	55
5.2.3.4	Rescue Therapy.....	56
5.3	Efficacy, Pharmacokinetic, Pharmacodynamic, Immunogenicity and Safety Assessments/Variables.....	57
5.3.1	Efficacy and Safety Measurements Assessed and Flow Chart	57
5.3.1.1	Study Procedures	65
5.3.2	Drug Concentration Measurements	86
5.3.3	Biomarker Measurements	87
5.3.4	Pharmacogenetic Measurements.....	87

5.3.4.1	Handling/Processing of Samples	88
5.3.4.1.1	Serum Adalimumab Concentration and AAA Analysis	88
5.3.4.1.2	Biomarker Analysis	89
5.3.4.1.3	Pharmacogenetic Analysis	89
5.3.4.2	Disposition of Samples	89
5.3.4.3	Measurement Methods.....	90
5.3.5	Efficacy Variables.....	90
5.3.5.1	Primary Efficacy Variables.....	90
5.3.5.2	Secondary Variables	90
5.3.5.3	Exploratory Variables	92
5.3.5.4	Pharmacokinetic Variables	92
5.3.5.5	Pharmacogenetic Variables.....	92
5.3.6	Safety Variables	93
5.4	Removal of Subjects from Therapy or Assessment.....	93
5.4.1	Discontinuation of Individual Subjects.....	93
5.4.2	Discontinuation of Entire Study.....	95
5.5	Treatments.....	95
5.5.1	Treatments Administered.....	95
5.5.2	Identity of Investigational Product.....	96
5.5.2.1	Packaging and Labeling.....	96
5.5.2.2	Storage and Disposition of Study Drug	97
5.5.3	Method of Assigning Subjects to Treatment Groups.....	97
5.5.4	Selection and Timing of Dose for Each Subject.....	98
5.5.5	Blinding.....	98
5.5.5.1	Blinding of Investigational Product	98
5.5.6	Treatment Compliance.....	99
5.5.7	Drug Accountability.....	99
5.6	Discussion and Justification of Study Design.....	100
5.6.1	Discussion of Study Design and Choice of Control Groups.....	100
5.6.2	Appropriateness of Measurements.....	101
5.6.3	Suitability of Subject Population	101
5.6.4	Selection of Doses in the Study	102
6.0	Complaints	102

6.1	Medical Complaints	103
6.1.1	Definitions.....	103
6.1.1.1	Adverse Event.....	103
6.1.1.2	Serious Adverse Events	104
6.1.2	Adverse Event Severity.....	105
6.1.3	Relationship to Study Drug.....	105
6.1.4	Adverse Event Collection Period.....	106
6.1.5	Adverse Event Reporting.....	107
6.1.6	Pregnancy.....	108
6.1.7	Toxicity Management	109
6.2	Product Complaint	109
6.2.1	Definition	109
6.2.2	Reporting.....	110
7.0	Protocol Deviations.....	110
8.0	Statistical Methods and Determination of Sample Size	112
8.1	Statistical and Analytical Plans.....	112
8.1.1	Analysis Population	112
8.1.2	Planned Methods of Statistical Analysis.....	112
8.1.3	Analysis of Demographic Data and Double-Blind Baseline Disease Characteristics and Other Analyses.....	113
8.1.4	Efficacy Analysis	113
8.1.4.1	Analysis for Primary Objective	113
8.1.4.2	Analysis for Secondary Objectives.....	114
8.1.4.3	Analysis for Exploratory Objectives.....	115
8.1.5	Pharmacokinetic Analyses	116
8.1.6	Safety Analysis	116
8.1.7	Interim Analysis for Double-Blind Baseline Characteristics.....	117
8.1.8	Compliance	117
8.2	Determination of Sample Size	117
8.3	Randomization Methods	119
9.0	Ethics.....	119

9.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	119
9.2	Ethical Conduct of the Study	120
9.3	Subject Information and Consent.....	120
10.0	Source Documents and Case Report Form Completion	121
10.1	Source Documents	121
10.2	Case Report Forms.....	122
10.3	Electronic Patient Reported Outcomes (ePROs)	123
11.0	Data Quality Assurance	124
12.0	Use of Information.....	124
13.0	Completion of the Study	124
14.0	Investigator's Agreement.....	126
15.0	Reference List	127

List of Tables

Table 1.	Study Activities.....	58
Table 2.	Clinical Laboratory Tests.....	82
Table 3.	Identity of Investigational Products	96
Table 4.	Sample Size Assumptions.....	119

List of Figures

Figure 1.	Study Design Schematic	38
Figure 2.	Adverse Event Collection	107

List of Appendices

Appendix A.	Responsibilities of the Clinical Investigator	139
Appendix B.	List of Protocol Signatories.....	141
Appendix C.	Injection Instructions – Pre-Filled Syringe – Sample	142
Appendix D.	Subject Dosing Diary – Sample	149

Appendix E.	Joint Evaluation Worksheet – Sample	152
Appendix F.	DAS28 Joint Assessment.....	154
Appendix G.	Health Assessment Questionnaire (HAQ-DI) – Sample.....	155
Appendix H.	FACIT-Fatigue Scale (Version 4) English Version – Sample.....	158
Appendix I.	Treatment Satisfaction Questionnaire for Medication (TSQM) – Sample.....	159
Appendix J.	Work Productivity and Activity Impairment (WPAI) – Sample	164
Appendix K.	Short Form-36 (SF-36) Health Survey Questionnaire – Sample	166
Appendix L.	RAPID-3 Questionnaire/Assessment (in office and at home) – Sample.....	179
Appendix M.	MRI Assessments and Scoring – Sample	180
Appendix N.	Ultrasound Assessments and Scoring – Sample	181
Appendix O.	ACR 1987 and the ACR/EULAR 2010 Criteria for Classifying RA	183
Appendix P.	Protocol Amendment: List of Changes.....	186

3.0 Introduction

3.1 Disease Overview

Rheumatoid arthritis (RA) is an autoimmune disorder with an estimated prevalence of approximately 1% in the population.¹ The economic burden of RA is significant, resulting from both direct and indirect costs for the patient, including lost work income.^{2,3} Over the last 15 years, the effectiveness of TNFi (tumor necrosis factor inhibitor) therapies in RA has been widely proven and the use of these agents both in early and established RA and for short and long-term treatment periods up to 10 years has been shown to improve disease course and halt structural progression.⁴⁻⁹

3.2 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system. It consists of 1,330 amino acids and has a molecular weight of approximately 148 kilodaltons. Adalimumab is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF- α but not to lymphotoxin- α .

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Adalimumab was first approved in the United States and European Union (EU) for the treatment of RA in 2002 and 2003, respectively. Additional indications have been approved in the United States and EU including psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis. Additional updates regarding approved indications can be found in the current edition of the Investigator Brochure.

3.3 Rationale for the Study

The treat to target recommendations advocate that the primary goal of treating subjects with RA is to maximize long-term Health Related Quality of Life (HRQoL) through control of symptoms, prevention of structural damage, normalization of function and social participation.¹ Abrogation of inflammation is the most important way to achieve these goals. The aimed targets have been defined as clinical remission or low disease activity (LDA), depending on disease duration and accumulated damage. The widespread use of (biological disease-modifying anti-rheumatic drugs) bDMARDs, mainly TNFi, helps patients to achieve these goals and thus have become an integral part of the standard of care of RA.^{10,11}

For patients treated with bDMARDs who achieve clinical remission, a question at the center of several recent clinical trials has been whether biologics need to be maintained at a stable dose or can be withdrawn or tapered. Even with an increasing introduction of these treatment regimens in routine clinical practice, the evidence supporting their effectiveness is equivocal. Furthermore, patient outcomes in early RA treated with initial combination of methotrexate (MTX) and aTNFi versus in established RA have been very different.^{12,13}

In early RA patients, controlled withdrawal studies have resulted in somehow different outcomes for different TNFi compounds: whilst the OPTIMA¹⁴ trial showed that the majority of early RA MTX-naïve patients in stable LDA were able to maintain disease control for 52 weeks after discontinuing adalimumab, in the PRIZE study,¹⁵ on the other

hand, withdrawing etanercept was associated with a higher number of patients losing their status of clinical remission.

In established RA, withdrawing TNFi or other bDMARDs has been associated with relapses or RA flares in a higher proportion of patients than in early RA.¹³ Data from both open-label uncontrolled studies¹⁶⁻¹⁹ and few controlled trials²⁰⁻²³ has indicated that in patients treated with bDMARDs after incomplete response to csDMARDs, discontinuation of the biologic therapy without triggering loss of disease control can only be achieved in some of them.

Research has also been conducted investigating the outcomes of TNFi dose tapering (dose reduction or increased interval of drug administration) treatment strategies in RA patients achieving the target of LDA or remission. Studies have shown that a certain proportion of patients can maintain remission following a tapering strategy for 48 weeks,²⁰ 54 weeks²¹ and up to 18 months.²⁴ However, the data show also that a considerable proportion of these patients experienced an RA flare or loss disease control following dose reduction.

Thus, despite the existing evidence on dose reduction in RA, several questions that are critical if considering the implementation of this practice in clinical practice remain unanswered:²⁵ Who are the patients who can maintain clinical control upon tapering? Which patient and or disease characteristics are predictive for the risk of flare versus the maintenance of response following a tapering regimen? Is it feasible to devise a patient selection strategy or algorithm to inform dose tapering in daily clinical care? Is re-institution of normal dose/dosing regimen of TNFi in case of flares effectively providing patients the same level of disease control they had before?

The overarching aim of the study we propose here is to attempt to provide answers to all these questions. The objectives of the study aim to study the association of patient characteristics, with a particular focus on residual inflammation, with the development of flares following a prevailing dose tapering strategy.

3.3.1 Additional Considerations on Key Study Parameters

Rheumatoid Arthritis Flares

The occurrence of flares, their detection, as well as their characterization has been subject of numerous studies. Several flare definitions have been proposed and have been submitted to validation analyses in the context of RA clinical trials.^{22,24,26} An increase in DAS28(ESR) higher than 1,2 has been accepted as being clinically meaningful representing a true worsening of the disease;²⁷ However, this definition of flare is often not capturing patients with meaningful disease activity.²⁸ A European Expert Consensus panel defined, for patients previously in clinical remission, a flare when an increase in DAS28 (ESR) of > 0.6 AND a DAS28 (ESR) > 2.6 occurs. Thus, in order to capture meaningful worsening of RA over time flare will be defined as an increase from dbBaseline in DAS28 (ESR) of > 0.6 AND a DAS28 (ESR) > 2.6 or an increase in DAS28 (ESR) of ≥ 1.2 irrespective of DAS28 (ESR).

Clinical Remission Defined by DAS28 < 2.6

DAS28 (CRP) has been validated in comparison with DAS28 (ESR) and data indicated that both measures are useful for assessing disease activity in patients with rheumatoid arthritis.²⁹ Accordingly, both scores can and have been included as an outcome variable in clinical trials, and have been used in clinical practice to define disease activity e.g., clinical remission (< 2.6). Despite the fact that both scores are reflecting accurately disease activity, the cut-off points for disease activity indexes, including clinical remission, might be slightly different for DAS28 (CRP): the percentage of patients meeting the definition of remission (< 2.6) might be slightly higher for DAS28-CRP than DAS28-ESR.^{30,31}

In clinical practice it's relatively frequent to use the also validated 3 variables DAS28³² or instead of the most widely used DAS28 4 variables due to difficulties on getting documented patient global assessment (PGA) in a Visual Analogue Scale (VAS). Moreover, a recent study has shown that despite the existence of individual patient baseline differences prior to treatment with TNFi, after 12 weeks of TNFi and particularly

for the lower range the 3 and 4 variables DAS28 (CRP).scores were similarly sensitive to change, highly correlated and the mean inter-score difference was very small.³³

Accordingly, for the purpose of identifying subjects on stable clinical remission for ≥ 6 months for Screening, both DAS28 (ESR) and (CRP) 4 or 3 (when PGA is not available) variables documented as being lower than 2.6 for at least 6 months prior to screening will be accepted. However, at Screening, only subjects with 4 variables DAS28 (ESR) < 2.6 may be enrolled and throughout the study clinical remission is defined by the 4 variables DAS28 (ESR) < 2.6 . Flare will be assessed based on DAS28 (ESR) evaluation at any time point throughout the study (with ESR measured in the same visit).

Concomitant Treatments for RA

The 2013 EULAR recommendations update propose that in RA patients who are in stable clinical remission particularly if also treated with concomitant csDMARDs(s) tapering a bDMARD is an option; the updated 2015 ACR guidelines also consider tapering RA treatments as an option for such a patient population. Both treatment recommendations acknowledge that more data on tapering is needed as part of a research agenda.

It is the aim of this study to assess, in subjects treated in real life clinical practice conditions who have DAS28 < 2.6 , if imaging-detected sub-clinical inflammation (and disease, patient and treatment patterns as well as adalimumab drug level characteristics) brings an additional benefit in predicting and informing clinicians about who has a higher risk of flare while treated with a reduced dose of adalimumab.

As this study goal is to include patients as treated in routine clinical practice, the patient population must be in line with both treatment recommendations and clinical practice. Accumulated data from registries and other real world evidence, such as CORRONA,³⁴ US healthcare insurance claims database,³⁵ BSRBR,³⁶ RABBIT,³⁷ Nor-DMARD³⁸ and ARTIS³⁹ are showing that around 30% – 34% of patients being treated with bDMARDs including TNFi are on monotherapy even if at initiation of the bDMARD the vast majority of patients were on combination therapy.⁴⁰ As such this study will include mainly patients who are in stable remission for more than 6 months as assessed by DAS28

< 2.6 and after at least 1 year of treatment with adalimumab with concomitant MTX for at least the last 12 weeks prior to inclusion; in order to be in line with the current clinical practice up to 20% of the study patient population may be composed of subjects who are not treated with concomitant stable MTX but instead are treated with other than MTX allowed csDMARDs or not treated with a csDMARD as long as this treatment regimen is stable for at least 12 weeks prior to Week 0.

Assessment of Residual Disease Activity Using Imaging Techniques

The use of sensitive imaging techniques, i.e., musculoskeletal ultrasonography (US) and magnetic resonance imaging (MRI) allows for the identification of residual inflammation, which has been correlated with structural damage progression and upcoming RA flares in patients in clinical remission.

US is an imaging technology increasingly used in rheumatologists' clinical practice. Among approximately 50% of subjects on TNFi with established clinical remission, ultrasound assessments have been able to detect remaining signals of synovitis in Power Doppler ultrasonography (PDUS).³² These PDUS signals have been shown to be associated with a risk for progression and/or relapse/flare in several clinical trials.³²⁻⁴⁶

Despite its high use and validity in local clinical settings, the use of US has been limited in large clinical trial settings due to inter-operator and inter-observer variability, and the significant dependence on the expertise on the ultrasound assessor.^{46,47}

MRI is a highly sensitive and standardized imaging technique suitable for clinical trials: Using MRI in RA has been shown to identify erosions otherwise not observed with conventional x-ray.⁴⁸ Similarly like US, MRI assessments have shown signs of inflammation by synovitis and bone marrow edema (BME) in a high proportion of patients considered in clinical remission.⁴⁹ It was further demonstrated that MRI signals of inflammation as detected by the Rheumatoid arthritis MRI scoring system (RAMRIS)⁵⁰ validated scores are correlated with structural progression as measured by conventional x-ray and are suggested to indicate remaining disease activity.^{49,51,52}

Current European League Against Rheumatism (EULAR) recommendations on the value of imaging for diagnosis and monitoring RA patients recognize the value of MRI as well as US on the diagnosis and monitoring of RA (besides conventional x-ray).⁵³ Nevertheless, MRI is not used in daily clinical practice to monitor RA and will not replace the clinical value for disease activity assessment and practicality of US nor the value of conventional x-ray for assessment of disease damage and structural progression. However, its high sensitivity and reproducibility as well as low inter-observer variability,⁵⁰ make it ideal for imaging detection of inflammation in a clinical trial setting.⁴⁸ In addition, in RA patients who are in stable clinical remission and subsequently taper or withdraw a bDMARD, MRI may detect potential bone and cartilage deterioration.

It is the primary objective of this study is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects submitted to an adalimumab dose tapering regimen controlled by adalimumab withdrawal.

Clinical Patient Characteristics

Several additional patient characteristics, some well proven as prognostic factors of more severe RA, have also been investigated in their potential association with the outcome of a tapering or withdrawal of TNFi treatment strategy; not limited but including the following parameters have, even if not consistently, been suggested to be potentially associated with loss of disease control upon a tapering strategy:^{11-13,17,21,25,54}

- Disease duration
- Rheumatoid factor (RF) and/or Anti-citrullinated peptide antibody (ACPA) positivity
- Erosive disease
- Smoking
- Initial disease activity
- Previous treatment with csDMARDs or bDMARDs

- Concomitant use of corticosteroids
- Duration of treatment and remission with the bDMARD
- CRP
- Health Assessment Questionnaire – Disability Index (HAQ-DI)

Patient clinical characteristics and their association with the occurrence of flares upon tapering of adalimumab controlled by its withdrawal will be assessed.

Drug Monitoring

A drug-related hypothesis relates to individual differences in serum drug concentrations: patients with higher trough concentrations would be more likely to remain in remission following a dose tapering regimen than patients with lower trough concentrations.^{55,56}

This concept has not been validated. On the contrary, it has been shown that there is a high range of individual variability in both clinical response and adalimumab trough concentrations⁵⁷ thus precluding recommendations for concentration-guided therapy (therapeutic drug monitoring).

Adalimumab trough concentrations at baseline and at several time points and their potential predictive value for flares will be investigated during this study.

Biomarkers

The potential predictive value of certain biomarkers for progressive destructive RA and their potential role in monitoring treatment response has been frequently investigated.⁵⁸⁻⁶⁰ So far, a biomarker or set of biomarkers which would predict RA clinical course or disease progression has not yet been identified. Recent findings suggest it may be possible to find surrogate serum biomarkers of active synovitis that could be useful in the follow-up of patients with RA in remission in order to identify risk of increase of disease activity.⁶¹⁻⁶⁴

Identification of biomarkers which may be of interest to understand the contributing factors for successful tapering are therefore part of the exploratory assessments of the study.

3.4 Safety Information

Adalimumab therapy has a well-established and well described safety profile based on extensive post marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an United States Food and Drug Administration (FDA)-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 6.1.5 under Adverse Event Reporting.

3.5 Differences Statement

This Phase 4 study is the first randomized, placebo-controlled, double-blind study, to evaluate the association between residual inflammation detected by MRI at Baseline and RA flares or maintenance of clinical remission outcome of a bDMARD dose tapering. The dbBaseline demographics and clinical patient characteristics, adalimumab drug levels, US detected joint inflammation and RA biomarkers and their association with the 36-week outcomes of adalimumab tapering will also be assessed. Open-label adalimumab 40 mg every other week (eow) rescue treatment for subjects experiencing a flare will be investigated.

3.6 Benefits and Risks

This study is being conducted in subjects previously treated with adalimumab for at least 12 months and who achieved stable clinical remission for at least 6 months. Thus, subjects enrolled have already been exposed to adalimumab.

The safety profile of adalimumab in RA and other approved indications is well established. Adverse events in the categories of autoimmunity, demyelinating disorders, congestive heart failure, gastrointestinal disorders, hematologic events, hepatic events, hypersensitivity, immunosuppression, infections, malignancies, respiratory thoracic disorders, and vascular disorders have been observed with adalimumab therapy.

The treatment interventions in this study, dose tapering and withdrawal, are treatment algorithms used in clinical practice:^{11,24,26,65-68} In this study, subjects will be randomized (5:1) to a reduced dose of adalimumab 40 mg subcutaneous (sc) every 3 weeks (q3wks) (taper arm) or matching placebo (withdrawal arm). Subjects will maintain a stable dose of MTX (any dose; oral, sc or im) and/or of any other additional concomitant RA medication as taken before enrollment into the study.

Subjects experiencing a flare at any time point will be switched to an Open-Label Rescue Arm and immediately provided adalimumab 40 mg eow for at least 16 weeks.

AbbVie expects the results from this study to provide treating health care professionals (HCPs) with additional evidence potentially useful in characterizing the profiles of patients that might be considered for a tapering strategy and to identify those that might be at risk of flaring if submitted to a dose or interval modification.

4.0 Study Objectives

The **primary objective** is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects randomized to an adalimumab dose tapering regimen controlled by adalimumab withdrawal.

The **Secondary Objectives** are:

- To assess the occurrence and severity of flares and the time to flares in both taper and withdrawal arms.
- To investigate the association between dbBaseline subject demographic and disease characteristics (and the occurrence of flares).
- To investigate the association between dbBaseline adalimumab trough concentrations and the occurrence of flares.
- To evaluate the effectiveness of rescue therapy with open-label adalimumab 40 mg every other week (eow) over 16 weeks in subjects experiencing a flare.
- To assess the change in rheumatoid arthritis MRI scoring system (RAMRIS) scores from Baseline to Final visit in the taper, withdrawal and Open-Label Rescue Arms.
- To investigate the MRI-flare associations in sub-groups of subjects who meet additional clinical remission criteria at dbBaseline including simplified disease activity index (SDAI) ≤ 3.3 , clinical diseases activity index (CDAI) ≤ 2.8 and ACR/EULAR 2011 boolean-based remission, as well as to describe the course of disease and patient reported outcome (PRO) measures in the taper, withdrawal and Open-Label Rescue Arms overall and per dbBaseline subgroup.
- To assess the rate of anti-adalimumab antibodies (AAA) positive subjects in the taper and withdrawal arms.

The study has also the following **exploratory objectives**:

- In the subgroup of subjects with a Baseline Ultrasound (US) assessment:
 - To investigate the association between Baseline ultrasound scores and the occurrence of RA flares.
 - To investigate the association between the Baseline ultrasound scores and Baseline MRI RAMRIS scores.
 - To describe the change in the ultrasound scores from Baseline to the time of RA flare in the taper and withdrawal arms.

- To investigate the association between biomarker values at dbBaseline (or their change over time) and the occurrence of flares.

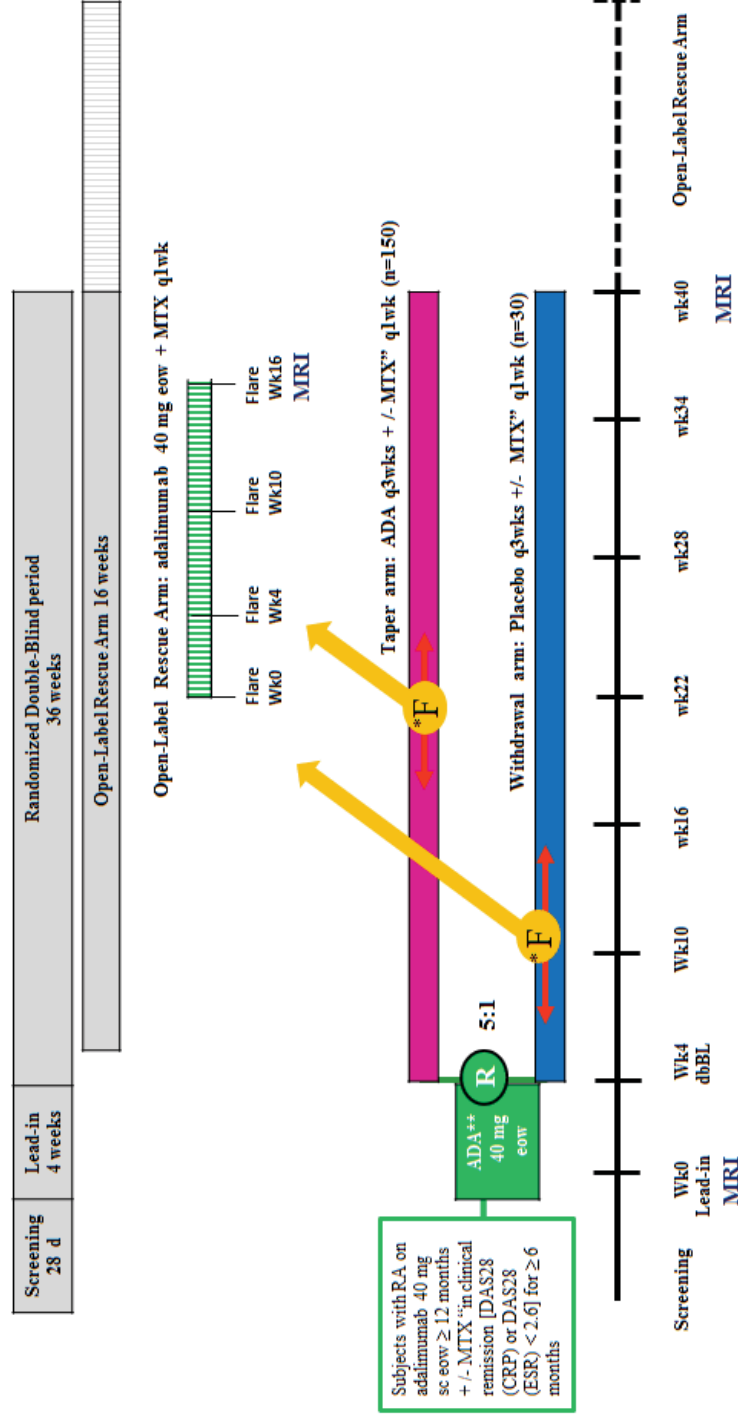
5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 4, multicenter, randomized, double-blind, parallel-group study. The study duration will include a Screening period of up to 28 days, a 4-week Lead-In Period with open-label 40 mg adalimumab eow and a 36-week Double-Blind Period with 40 mg adalimumab/placebo q3wks; subjects who experience a flare at any time will enter a Rescue Arm and will be followed for 16 weeks.

The study design schematic is presented in [Figure 1](#).

Figure 1. Study Design Schematic



* Flare at any time point; Flare defined as: DAS28 (ESR) ≥ 2.6 AND an increase in DAS by > 0.6 OR an increase in DAS28 (ESR) by ≥ 1.2 from dbBaseline irrespective of DAS28(ESR); Subjects who flare at any time during the randomized Double-Blind period will be switched to OL ADA 40 mg eow and continue in the Open-Label Rescue Arm for 16 weeks up to a maximum study duration of 56 weeks.

** ADA = adalimumab

“ at least 80 % of patients in combination treatment with stable MTX ≥ 12 weeks; up to 20% on stable other csDMARDs or adalimumab monotherapy ≥ 12 weeks

Screening Period (up to 28 days):

At the Screening Visit, prior to the Lead-In Period, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the Screening procedures outlined in [Table 1](#). The Screening period may be exceptionally extended beyond 28 days upon justification and further consultation with Study Designated Physician. The target population for the study consists of RA subjects on adalimumab treatment for at least 12 months and in stable clinical remission, as defined by a 4 or 3 (whenever PGA is not available) variables DAS28 (CRP) or DAS28 (ESR) < 2.6 for at least 6 months prior to the Screening Visit, in combination with MTX (at a stable dose for ≥ 12 weeks prior to Week 0 Visit) or if not on MTX, in other allowed csDMARDs at a stable dose or not treated with a csDMARD for ≥ 12 weeks prior to Week 0 Visit. Subjects with a documented DAS28 (CRP) or (ESR) < 2.6 (or availability of the 4 or at least 3 components that allow for calculation of a DAS28 score) at least 6 months prior to Screening Visit may be screened. However, for enrollment and throughout the study clinical remission will be defined by 4 variables DAS28 (ESR) < 2.6 criteria.

All screened subjects satisfying all the inclusion (including a DAS28 [ESR] assessment of < 2.6 evaluated at Screening) and none of the exclusion criteria will be enrolled into the study. Confirmation of a DAS28 (ESR) < 2.6 assessed at the Screening and at the Week 0 Visit is required prior to subject inclusion into the Lead-In Period.

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. All Screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial Screening evaluation including the assessment of a purified protein derivative (PPD) test (or equivalent), or Interferon-Gamma Release Assay (IGRA; QuantiFERON-Tuberculosis [TB] Gold In-Tube test or T-SPOT TB test), chest x-ray and ECG, these tests will not be required to be repeated for re-screening provided the conditions noted in [Section 5.3.1.1](#)

are met and no more than 12 months have passed. As appropriate, sites are encouraged to contact the AbbVie Study Designated Physician to confirm if subjects should or should not be re-screened. If the re-screening visit is occurring within 4 weeks of last screening some other procedures may not be required upon discussion and agreement with Study Designated Physician.

Lead-In Period (4 Weeks):

Subjects who fulfill all Screening criteria will enter the study with a 4-week Lead-In OL Period: subjects will receive adalimumab 40 mg sc eow starting at Week 0 of the Lead-In Period. Week 0 will occur 2 weeks after the subject's last dose of commercial Humira[®] (± 2 days) to keep in line with eow dosing. At the Week 0 visit subjects will undergo the corresponding procedures as outlined in [Table 1](#) including DAS28 (ESR) assessment to confirm remission using the ESR result from the same day of the visit. If the subject enrollment is confirmed at the Week 0 visit, the subject will stop commercial Humira[®] and initiate adalimumab investigational product open-label sc. The first sc injection will be administered at the site at the end of the visit; the second injection will be given 14 days thereafter (± 3 days) and every other week (± 3 days) until Week 4 dbBaseline Visit. If needed the subject may be assisted by the study team for the self-injection of the syringe. Subjects must undergo a high-field contrast MRI scan of the most affected hand (2nd to 5th MCP) and wrist during the Lead-In Period. If both sides are considered equally affected the MRI of the dominant hand (2nd to 5th MCP) and wrist will be performed.

MRI images will be read centrally. Further details regarding MRI requirements, procedures and central reading will be provided in an MRI manual. The assessors will be blinded to the clinical assessments and the clinical Investigator will be blinded to the MRI assessments performed centrally. A local report for safety reasons on urgent and RA inflammation related findings other than RA may be viewed by the investigator. The dbBaseline Visit and randomization are not dependent on the results or report of the central reader. **Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.**

Sites will be asked at study-start if they want to participate and if they qualify for the optional US assessment, according to requirement described in [Appendix N](#) and in the US manual. Sites that participate in US assessments will need to nominate a qualified Ultrasonographer to perform and locally assess the US during the Lead-In period or at the dbBaseline Visit; there will not be a central reading of the US images. The Ultrasonographer will be blinded to the clinical assessments and the clinical Investigator will be blinded to the ultrasound assessments.

If needed for procedural compliance (e.g., to allow MRI and its certification, for injection scheduling adjustment), the lead-in period can be extended up to 2 more weeks in which case the DAS28 (ESR) assessment and all the dbBaseline Week 4 Visit study procedures will occur up to 6 weeks after the Week 0 Visit. These cases or other exceptions related with further extension of the Lead-in period should be discussed with the Study Designated Physician.

Double-Blind Period:

A confirmed adequate MRI from the Lead-In Period is required before the dbBaseline visit. At the end of the Lead-In Period, subjects will be assessed again for DAS28 (ESR) at the dbBaseline Week 4 visit. At the Week 4 visit, if the subject does not meet the DAS28 (ESR) of < 2.6 or if the subject is unable to obtain confirmed and certified MRI scan images, the subject would need to be discontinued from the study at an Early Termination visit.

Subjects with a confirmed DAS28 (ESR) of < 2.6 at the dbBaseline visit, and as such fulfilling confirmed DAS28 (ESR) remission at 2 time points: Day 1 of Lead-In and 4 weeks later (or, exceptionally later) at the dbBaseline visit, will be randomized in a 5:1 ratio to one of two double-blind arms and followed for an additional 36 weeks:

1. a reduced frequency of adalimumab 40 mg sc to every 3 weeks (q3wks) (taper arm), or
2. adalimumab placebo sc q3wks: withdrawal arm.

The randomized Double-Blind period will begin at the dbBaseline Visit (Week 4) and will continue with visits every 6 weeks until the Week 40 Visit. The Week 40 visit will be considered the Final Visit.

At each scheduled visit during the double-blind period subjects will undergo the corresponding procedures as outlined in Table 1. The initial assessments at each of these visits must include ESR assessment except if the blood puncture for this procedure is very painful (in which case subjects should first fulfill the patient questionnaires); if the calculated DAS score meets flare criteria described below, the visit then becomes a Flare Week 0 Visit; and the stipulated procedures are completed.

Visits, including the dbBaseline Visit should aim to be scheduled in line with the injection date (± 3 days); in this case, subjects should be reminded not to take their scheduled injection prior to coming for the visit. The injections scheduled at the visits should occur at the site at the end of the visit.

During the interval between scheduled visits, subjects will be asked to contact their physicians in case they feel their disease is worsening: an unscheduled visit will be performed within 2 weeks of contact with the site to assess if subjects are experiencing a flare.

For any subject missing 2 consecutive visits within the Double-Blind Period, the site must contact the AbbVie Study Designated Physician regarding the subject's continued participation in the study.

No study drug will be administered or injected at the Final Visit.

Flare at Scheduled Visit:

If during a scheduled visit a flare (defined by DAS28 [ESR] > 2.6 AND an increase from dbBaseline in DAS28 [ESR] > 0.6 or increase of DAS28 [ESR] ≥ 1.2 from dbBaseline DAS28 [ESR] score irrespective of DAS28 [ESR]) is confirmed, the regular visit will then turn into a Flare Week 0 Visit.

At the Flare Week 0 Visit, subjects will undergo further study procedures as described in [Table 1](#) under Scheduled/Unscheduled Flare Week 0 Visit and will be switched to Open-Label Rescue Arm starting with the first OL injection of adalimumab 40 mg sc at the end of the visit. Subjects will be given at-home Routine Assessment of Patient Index Data (RAPID)-3 questionnaires (for self-assessment of disease activity) for weekly completion to be returned at every visit until the Flare Week 16 Visit.

Unscheduled Visit:

Subjects should be instructed (at every office visit) to contact the site if they feel their disease is worsening and will receive those instructions in the patient card. If a subject contacts the site due to possible worsening of RA, an unscheduled visit to confirm his/her clinical status within 2 weeks of contact with the site. Study procedures outlined in [Table 1](#) should be followed including an initial DAS28 (ESR) assessment. If a flare is not confirmed, the Unscheduled Visit is concluded and the subject will continue the regular scheduling of the Double-Blind Period Visits.

If a flare is confirmed, the unscheduled visit will turn into the Flare Week 0 Visit.

Flare at Unscheduled Visit:

At the Flare Week 0 visit subjects will undergo further study procedures as described in [Table 1](#) under Scheduled/Unscheduled Flare Week 0 Visit and will be switched to the Open Label Rescue Arm starting with the first adalimumab 40 mg sc OL injection at the end of the visit if last study drug injection has occurred more than 1 day ago. If not, OL adalimumab 40 mg will be provided for at home sc injection starting the next day.

Open-Label Rescue Arm

In the open-label Rescue Arm subjects will receive OL therapy with adalimumab 40 mg eow. After the first OL injection, adalimumab 40 mg will be administered sc eow. Subjects will be given RAPID 3 questionnaires (for self-assessment of disease activity) for weekly completion to be returned at every visit until the Flare Week 16 Visit.

All subjects will have 16 weeks of follow-up in the Open-Label Rescue Arm.

The Flare Week 16 Visit will be the Final Visit.

During the Open-Label Rescue Arm, it is at the Investigator's discretion to initiate or change the subject's following RA concomitant medications:

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Analgesics
- Corticosteroids (a dose up to a maximum of 15 mg oral prednisolone or equivalent/day and/or up to 3 injections intra-articular (i.a.) within the follow-up period of 16 weeks)
- csDMARDs including MTX (initiation and/or dose or administration mode change) and excluding csDMARDs that are not allowed (e.g., azathioprine, cyclophosphamide, d-penicilamine)

Joints submitted to an i.a. injection of corticosteroids within the last 4 weeks prior to a visit will be excluded from the tender and swollen joint evaluation. Four weeks after an i.a. injection, joints must be again evaluated and included in the scores.

All concomitant medications should be documented in the electronic Case Report Form (eCRF). If additional RA medications are required, the Study Designated Physician must be contacted.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination Visit.

Early Termination Visit

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects who prematurely discontinue while on the double blind and/or OL rescue period should complete the procedures outlined for the Early Termination/Final Visit in [Table 1](#) as soon as possible after the last dose of study drug and preferably prior to the administration of new therapies.

If subjects discontinue the study during the lead-in observational period from Week 0 up to Week 4, prior to randomization, a shortened Early Termination visit is required for: returning study material and drug, assess any safety/adverse events, collect reason for discontinuation. A 70-day follow-up call/visit will be required; the remainder of full Early Termination Visit study procedures can be completed per the investigator's discretion.

All subjects discontinuing the study will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events.

5.2 Selection of Study Population

Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 200 subjects will be enrolled into the Lead-In Period. The study is designed to randomize approximately 180 subjects in the Double-Blind Period to meet primary objective evaluation without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in Screening will not be enrolled.

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

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets all of the following criteria:

1. Male or female subjects \geq 18 years of age.
2. Subject has a diagnosis of RA as defined by the 1987 revised ACR classification criteria and/or the ACR /EULAR 2010 classification criteria (any duration since diagnosis).

3. Subject must meet the following criteria:
 - Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Week 0 Visit;
 - Must be treated with concomitant MTX in a stable dose (oral, sc or im at any dose) for at least 12 weeks prior to Week 0 Visit or if not on MTX, must be treated with other allowed csDMARDs at stable dose for at least 12 weeks prior to Week 0 Visit or if not treated with csDMARDs must maintain this regimen for at least 12 weeks prior to Week 0 Visit.
4. Subject must be in sustained clinical remission based on the following:
 - At least one documented 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) < 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
 - 4 variables DAS28 (ESR) assessed at Screening < 2.6 (with all components including ESR assessed at Screening).
5. If subjects are receiving allowed concomitant csDMARDs (in addition or not to MTX) the dose must be stable for at least 12 weeks prior to the Week 0 Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
6. If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to Week 0 visit.
7. If subjects are receiving concomitant NSAIDs, tramadol or other equivalent opioids and/or non-opioid analgesics the dose and/or therapeutic scheme must be stable for at least 4 weeks prior to the Week 0 Visit.
8. If female subject, is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing

an approved method of birth control throughout the study and for 150 days after last dose of study drug.

Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly include the following (see local informed consent for more detail):

- Oral (except for low-dose progestin-only [lynestrenol and norethisteron]), injectable or implanted hormonal contraceptives started for 90 days prior to study drug administration;
 - Intrauterine device (IUD);
 - Intrauterine system (for example, progestin-releasing coil);
 - A vasectomized male partner;
 - Abstinence from vaginal intercourse (when in line with preferred and usual lifestyle of the subject)
9. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, performed during Screening and based on documented 12-lead ECG and x-ray performed within 12 months prior to dbBaseline or if not available or documented, performed at Screening.
10. Subject is judged to have no contra-indications for the use of adalimumab as determined by the Investigator.
11. Subject has a documented negative TB Screening assessment within 12 months prior to Screening Visit or if latent TB infection, subject has had a minimum of 2 weeks (or per local guidelines whichever is longer) of TB prophylaxis prior to treatment with adalimumab and had or is completing a full course of TB prophylaxis.

If these requirements are not met, subject must perform a TB screening assessment: subject has a negative TB screening assessment and if there is a strong suspicion of TB exposure the subject must be evaluated by a TB expert (Section 5.3.1.1). If the

subject has evidence of latent TB infection, the subject must initiate and complete at least the first 2 weeks (or per local guidelines whichever is longer) of TB prophylaxis prior to Week 0.

12. Subjects must be able and willing to self-administer SC injections or have a qualified person available to administer SC injections.
13. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Rationale for Inclusion Criteria

- 1 – 7 To select the adequate subject population for this study disease.
- 9 – 12 For the safety of the study subjects.
- 8 The impact of adalimumab on pregnancies is unknown.
- 13 In accordance with harmonized GCP.

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. Any 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit ≥ 2.6 .
2. Subject is on an additional concomitant bDMARD (including but not limited to abatacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab or tocilizumab).
3. Subject has been treated with intra-articular or parenteral administration of corticosteroids within the last 4 weeks before Screening.
4. Subject has undergone joint surgery within 12 weeks of Screening (at joints to be assessed by MRI and/or ultrasound).

5. Subject has a history of chronic arthritis diagnosed before age 16 years, and history of gout, psoriatic arthritis or other rheumatic inflammatory disease apart from RA.
6. Subject has a medical condition precluding an MRI (e.g., magnetic activated implanted devices – cardiac pace-maker, insulin pump, neurostimulators, etc. and metallic devices or fragments or clips in the eye, brain or spinal canal and in the hand/wrist undergoing MRI).
7. Subject has a medical condition precluding a contrast MRI with gadolinium (i.e., nephrogenic systemic fibrosis, previous anaphylactic/anaphylactoid reaction to gadolinium containing contrast agent, pregnancy or breastfeeding, severe renal insufficiency with an estimated Glomerular Filtration Rate [eGFR] below 30 mL/min/1.73 m², hepato-renal syndrome, severe chronic liver function impairment).
8. Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Screening Visit.
9. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Screening Visit or oral anti-infectives within 14 days prior to the Screening Visit.
10. Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (PML) (i.e., natalizumab [Tysabri[®]], rituximab [Rituxan[®]], or efalizumab [Raptiva[®]]) or prior treatment with cyclophosphamide.
11. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
12. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency virus (HIV).
13. Subjects with any active viral infection that based on the Investigator's clinical assessment make the subject an unsuitable candidate for the study.

14. Hepatitis B: HBs Ag positive (+) or detected sensitivity on the hepatitis B (HBV)-DNA PCR qualitative test for HBc Ab/HBs Ab positive subjects (Section 5.3.1.1).
15. Chronic recurring infections or active TB.
16. Subject currently uses or plans to use anti-retroviral therapy at any time during the study period.
17. History of moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study.
18. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
19. History of clinically significant drug or alcohol abuse in the last 12 months.
20. Clinically significant abnormal screening laboratory results as evaluated by the Investigator.
21. Positive pregnancy test at Screening or Week 0.
22. Female subjects who are breastfeeding or considering becoming pregnant during the study.
23. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Rationale for Exclusion Criteria

- | | |
|------------|--|
| 1 – 5 | To select the adequate subject population for this study |
| 6 – 20, 23 | For the safety of the study subjects |
| 21, 22 | The impact of adalimumab on pregnancies is unknown |

The Investigator should contact the AbbVie study designated physician if there are any questions regarding inclusion and exclusion criteria and eligibility.

5.2.3 Prior and Concomitant Therapy

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

The AbbVie Study Designated Physician identified in Section 6.1.5 Adverse Event Reporting should be contacted if there are any questions regarding concomitant or prior therapies.

In addition for subjects age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, anti-neoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

5.2.3.1 Prior Therapy

All prior drug therapies for RA including csDMARDs and bDMARDs since initial diagnosis, must be recorded on the source documents and on the appropriate eCRF along with the dates of first and last dose, dosage/maximum dosage taken, route of administration and reason for use and for discontinuation, if known.

For each subject that is screened for the study, any other medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) taken 4 weeks prior to Week 0 Visit and throughout the end of the study must be recorded on the appropriate eCRF along with the date(s) of administration, reason for use, dosage, route and frequency.

Adalimumab use for ≥ 12 months prior to Week 0 Visit is required per protocol; date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF. A maximum of 2 non-consecutive adalimumab injections could have been skipped over the last 12 months but not during the 12 weeks prior to the Week 0 Visit. Reason(s) for a previously missed dose should be documented and cannot be due to an intentional tapering of medication (e.g., infection, surgery, lack of medication). Also there must be no evidence of $\text{DAS28} \geq 2.6$ during the last 6 months prior to screening as per exclusion criteria. A discussion with Study Designated Physician is recommended. MTX use at a stable dose (any dose; oral, sc or im) for ≥ 12 weeks prior to Week 0 Visit is required for at least 80% of subjects recruited; for those subjects on concomitant MTX, date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF. A decrease in the dose of MTX due to an event of tolerability (or other safety) related with MTX is allowed during the 12 weeks period prior to the Week 0 Visit and throughout the study as long as well documented.

Subjects who are not taking MTX in a stable dose for ≥ 12 weeks prior to Week 0 can be enrolled (up to 20% of overall study population) as long as their allowed csDMARD treatment has been stable for at least 12 weeks prior to Week 0 or if not treated with a csDMARD this regimen is stable for at least 12 weeks prior to Week 0 Visit. In these cases, csDMARD date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity

assessments (if available) should be documented and must be recorded on the appropriate eCRF. A decrease in the dose of csDMARD due to an event of tolerability or other safety related is allowed during the 12 weeks period prior to the Week 0 Visit and throughout the study as long as well documented.

When no csDMARDs has been used for at least 12 weeks prior to Week 0 Visit, date and reasons for stopping previous csDMARDs must be recorded in the eCRF. The allowed RA concomitant medications should be kept stable throughout the Lead-In and Double-Blind Periods of the study.

5.2.3.2 Concomitant Therapy

Each vaccine and all medications except study drug, administered to a subject during the study should be recorded in the eCRF as a concomitant medication. All concomitant medications will be provided by local prescription.

Methotrexate:

All subjects who were on MTX at inclusion must maintain a stable dose (any dose; oral, intra-muscular or sc) from the 12 weeks prior to Week 0 Visit and throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues related with MTX, the doses can be decreased and/or resumed as needed during the study and these changes documented.

Other Disease-Modifying Antirheumatic Drugs (DMARDs), Corticosteroids or Other Medications for RA:

Allowed other concomitant csDMARDs (chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and leflunomide) must be at a stable dose for at least 12 weeks prior to Week 0 Visit and at a stable dose throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues related with the csDMARDs, the doses can be decreased and/or resumed as needed during the study and these changes documented.

Concomitant use of oral corticosteroids (< 10 mg/day oral prednisone or equivalent) is allowed during the study and should be kept at a stable dose from 4 weeks prior to Week 0 Visit and throughout the study in the randomized double-blind arms.

Concomitant use of oral NSAIDs, tramadol or other equivalent opioids and non-opioid analgesics is allowed during the study and should be kept at a stable dose and/or therapeutic scheme from 4 weeks prior to Week 0 Visit and throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues, the doses of NSAIDs may be skipped, decreased and/or resumed as many times as needed during the study. On the days that subjects are scheduled to be seen in clinic, no regularly scheduled NSAIDs should be used within 12 hours of the subject's clinic visit.

Doses of all the RA treatment concomitant medications must remain stable throughout study participation (except as medically required due to an AE and in the rescue therapy arm; Section 5.3.4.1.2).

Folic acid supplementation during the study treatment period: All subjects treated with concomitant MTX should take a dietary supplement of oral folic acid 5 mg once weekly or per local guidelines per the investigator's discretion throughout the treatment period. Folate should not be administered on the day that MTX study medication is taken, nor on the following day.

For subjects who require isoniazid (INH) for TB prophylaxis consideration should be given to administer pyridoxine (Vitamin B₆) to prevent peripheral neuropathy.

MTX, folic acid and any other concomitant RA medications will be received by local prescriptions.

The AbbVie Study Designated Physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.3 Prohibited Therapy

The following are prohibited medications during the study:

- All bDMARDs with a potential therapeutic impact on the disease being studied including but not limited to the following:
 - Infliximab (Remicade[®]);
 - Etanercept (Enbrel[®]);
 - Ustekinumab (Stelara[®]);
 - Natalizumab (Tysabri[®]);
 - Anakinra (Kineret[®]);
 - Abatacept (Orencia[®]);
 - Rituximab (Rituxan[®]);
 - Tocilizumab (Actemra[®]);
 - Golimumab (Simponi[®]);
 - Certolizumab (Cimzia[®]);
 - Belimumab (Benlysta[®]);
 - Infliximab biosimilar(s) (Remsima[®], Inflectra[®]).
- Live vaccines (during the study and for 70 days after the last dose of study drug).
- Rifampin/Pyrazinamide combination.
- Anti-retroviral therapy.
- Other than allowed csDMARDs (e.g., azathioprine, cyclophosphamide, d-penicillamine).
- Opioid analgesics (other than tramadol or other equivalent opioid analgesics) or marijuana.
- Any investigational drug of chemical or biologic nature.
- Medications that may have potential for drug interaction with MTX should be administered with caution and careful ongoing monitoring.

On the days that subjects are scheduled to be seen in clinic, no opiates/analgesics (including regularly scheduled NSAIDs) should be used within 12 hours of the subject's clinic visit.

Subjects may be discontinued from the study if any of the above prohibited medications are used during the study.

Contact the AbbVie Study Designated Physician identified in Section 6.1.5 if there are any questions regarding prohibited therapy(ies).

5.2.3.4 Rescue Therapy

The Open-Label Rescue Arm consists of adalimumab 40 mg eow as detailed in Section 5.1.

During the Open-Label Rescue Arm, it is at the Investigator's discretion to initiate or change the subject's following concomitant medications for RA:

- NSAIDs
- Analgesics
- Corticosteroids (in a dose up to a maximum of 15 mg oral prednisolone or equivalent/day and up to 3 injections i.a. within the follow-up period of 16 weeks)
- csDMARDs including MTX (initiation and/or dose or administration mode change) and excluding not allowed csDMARDs (e.g., azathioprine, cyclophosphamide, d-penicilamine)

All concomitant medications should be documented in the eCRF. If additional RA medications are required, the Study Designated Physician must be contacted.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Immunogenicity and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Subjects will be allowed a visit window of ± 7 days for all study visits (with the exception of the Screening Period, Lead-In Period and the dbBaseline Visit). For the lead-in period and the dbBaseline period a visit window of ± 3 days is recommended. For exceptional cases, the Study designated Physician should be consulted. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Week 0) between Weeks 0 and 4 Visits. Once the subject is randomized, all doses should be based on the date of randomization (Week 4).

All study data will be recorded in the source documents and on the appropriate eCRF.

Study procedures will be performed as outlined in the schematic presented in [Table 1](#).

Table 1. Study Activities

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare							Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0					70-Day F/U Visit/ Call		
			Week							Flare Week							
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4	10	16	ET ^d		UV	
Informed Consent	X																
Inclusion/Exclusion Criteria	X	X ^b															
Medical History	X	X															
Alcohol and Nicotine Use	X																
Full Physical Exam	X	X															
Symptom-directed Physical Exam			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs/Weight/ Height ^c	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
28 and 66 – Swollen Joint Count (SJC)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
28 and 68 – Tender Joint Count (TJC)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment (PhGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare							Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0					70-Day F/U Visit/ Call					
			Week							Flare Week										
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4	10	16	ET ^d		UV				
Patient's Global Assessment (PGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pain Visual Analog Scale (VAS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep Disturbance VAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stiffness Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Flare Severity Assessment																				
DAS28 (ESR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Assessment Questionnaire – Disability Index (HAQ-DI)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-fatigue)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare							Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0					70-Day F/U Visit/ Call		
			Week							Flare Week							
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4	10	16	ET ^d		UV	
Treatment Satisfaction Questionnaire for Medication (TSQM)			X		X		X		X			X		X			
Work Productivity and Activity Impairment (WPAI)			X				X				X		X				
Short Form-36 (SF-36)			X				X				X		X				
Routine Assessment of Patient Index Data (RAPID-3)		X	X		X		X		X		X		X				
RAPID-3 for at Home Disease Assessment													X ^e				
Ultrasound Assessment													X ^f				
Electro Cardiogram (ECG)	X ^g																
Chest X-ray (CXR)	X ^g																
MRI		X ^j													X ^{h,i}		X ^{h,i}

Table 1. Study Activities (Continued)

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare								Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0					70-Day F/U Visit/ Call	
			Week								Flare Week						
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4	10	16	ET ^d	UV		
TB Screening ^l	X ^g																
HBV Screening	X ^g																
Pregnancy Tests	X ^k	X ^l															
Chemistry/Hematology	X	X		X		X		X		X		X		X			
ESR	X	X		X		X		X		X		X		X			
CRP	X	X		X		X		X		X		X		X			
RF/ACPA				X						X				X			
Biomarkers ^q				X				X		X		X		X			
Optional Biomarkers for additional research ^q				X		X		X		X		X		X			
Optional Pharmacogenetic (PG) Sample-DNA ^m				X								X		X			
Optional Pharmacogenetic Sample – ribonucleic acid (RNA) ^m				X		X		X		X		X		X			

Table 1. Study Activities (Continued)

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare							Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0				70-Day F/U Visit/ Call		
			Week							Flare Week					ET ^d	UV
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4	10	16			
Blood samples for PK ⁿ			X	X	X	X	X	X	X	X	X	X	X	X		
Blood samples for AAA ⁿ			X	X	X	X	X	X	X	X	X	X	X	X		
Antinuclear antibodies (ANA)/Double stranded deoxyribonucleic acid (dsDNA)	X													X		
Urinalysis ^o	X		X	X	X	X	X	X	X	X	X	X	X	X		
Monitor Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Therapy Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment		X														
Randomization			X													
Dispense Study Drug		X	X ^f	X	X	X	X	X	X	X	X	X	X	X	X	X

dbBaseline = Double-Blind Baseline; ET = Early Termination; UV = Unscheduled Visit; F/U = Follow-Up

Table 1. Study Activities (Continued)

- a. Screening must include a documented DAS28 (ESR) assessment prior to the Lead-In Period. An additional DAS28 (ESR) assessment must be completed at dbBaseline Week 4 in the Lead-In Period to confirm inclusion in the trial.
- b. Before study drug administration, all inclusion and exclusion criteria should be re-confirmed based on assessments completed during the Screening period.
- c. Height will be measured at Screening only. Weight will be measured at Screening and Final/Early Termination Visit.
- d. For those subjects who have entered the study at Week 0 but are early terminated before the Week 4 visit, a short Early Termination visit is allowed. This visit would include reason for discontinuation, review of adverse events, and investigational product/diary return. This will be followed by a 70-day follow-up call/visit. Additional assessments are allowed per the Investigator's discretion.
- e. Subjects are given a questionnaire to take home and fill out every week after flaring to be returned to the site at each visit.
- f. US Gray Scale and Power Doppler with a systematic longitudinal and transverse multiplanar examination of 46 joints and 18 tendon/tendon compartments. US will be performed on all subjects at sites that participate in the US assessment. Ultrasound can be performed in the Lead-In Period or at the Double-Blind Baseline Visit prior to randomization.
- g. Not required if subject has documented assessment within 12 months of Screening and meets inclusion and none of the exclusion criteria. If there is no evidence or if there is doubt in the results, then they need to be assessed at Screening. A CXR may be required for evaluation of active TB.
- h. To be completed if ≥ 12 weeks after last MRI.
- i. High-field adequate contrast MRI of the most affected or dominant hand (2 – 5 metacarpophalangeal joints [MCP]) and wrist (if both sides are considered equally affected) must be confirmed at dbBaseline that it was received and marked as complete by the Central Reader.
- j. A repeat TB test must be performed one year after the date of the previous test (± 2 months). The repeat TB test can occur at any visit.
- k. All females of childbearing potential will have a serum pregnancy test at Screening.
- l. All females of childbearing potential will have a urine sample collected at the Week 0 visit prior to study enrollment and at study discontinuation/completion. The samples will be tested locally by designated study personnel. Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study. Investigators may conduct more frequent urine pregnancy testing as necessary according to their judgment.
- m. Subjects will sign a separate informed consent if they agree to participate in pharmacogenetic research.
- n. PK and AAA samples are to be drawn prior to study drug injection.
- o. Dipstick urinalysis will be completed by the central lab at all required visits. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

Table 1. Study Activities (Continued)

- p. If the subject has a confirmed flare in a scheduled or unscheduled visit during the Double-Blind Period, this visit then becomes the Flare Week 0 Visit.
- q. Biomarkers are to be drawn prior to study drug injection and will be evaluated per [Table 2](#). Additionally, (and only for subjects who consent) samples will be banked for future research.
- r. The dbBaseline injection should occur at the site.

5.3.1.1 Study Procedures

General Guidance for Visits

At any visit, the study procedures must always start with the ESR blood test (except for the Screening Visit when the Informed Consent must be obtained) so that within the time frame of the visit the result will be used for the DAS28 (ESR) assessment.

Informed Consent

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific informed consent will be reviewed, signed and dated by the subject or their legally authorized representative before any study-related procedures are undertaken, or before any medications are withheld from the subject in order to participate in this study. Participation in further then pre-specified biomarker research analysis is optional, as indicated in the main consent. A separate consent is required from each subject in order to participate in the optional pharmacogenetic analysis. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

Subject will be eligible for study enrollment if he/she meets all inclusion criteria and none of the exclusion criteria at both the Screening and Week 0 of the Lead-In Period.

At the dbBaseline Visit (Week 4), in order for the subject to be randomized, another 4 variables DAS28 (ESR) must be completed and fulfill the requirement of < 2.6 . The ESR from the dbBaseline Visit must be used for this assessment. If the subject does not meet the DAS28 (ESR) requirement of < 2.6 at the dbBaseline (Week 4), the subject must be discontinued from the trial.

Medical and Surgical History

A complete non-RA related and/or co-morbidities medical and surgical history, as well as history of tobacco and alcohol use, will be obtained from each subject during the Screening Visit. A list of each subject's specific RA related medical and surgical history,

including disease duration, prior treatments, disease activity at diagnosis (if available) and at initiation of adalimumab, time to and duration of remission after initiating adalimumab, time on adalimumab, should be recorded at Screening. Additionally, if available from the last 12 months, detailed documentation referring to TB screening and/or liver transportation (LT) prophylaxis, chest x-ray, ECG and hepatitis B screening will be recorded at Screening. An updated medical history will be obtained prior to study drug administration at Day 1 of Lead-In and updated as necessary throughout the study on the eCRF.

A detailed medical history with respect to TB exposure needs to be documented. This information needs to include Bacillus Calmette-Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations.

Physical Examination

A complete physical exam will be performed at the designated study visits in [Table 1](#). Physical examination findings that are related or part of each subject's medical history should be captured on the appropriate eCRF page. The physical exam at the dbBaseline Visit will serve as the dbBaseline exam for the entire study.

A symptom-directed physical examination can be performed at any other visits if, in the opinion of the Investigator, it is warranted by the subject's AE status or on review of symptoms. Any clinically significant physical examination findings after dosing should be recorded as adverse events.

Vital Signs/Weight/Height

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate and body temperature will be obtained at each visit. Each subject's height will be measured at the Screening Visit only. Each subject's weight will be measured at the Screening and Final/Early Termination visits. All measurements will be recorded in metric units where applicable.

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

Swollen Joint Count

An exam of 66 joints ([Appendix E](#)) will be performed at the Screening Visit and all subsequent study visits. 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"). For DAS28 (ESR) calculation, the 28 joints assessment will be used ([Appendix F](#)).

Tender Joint Count

An exam of 68 joints ([Appendix E](#)) will be performed at the Screening Visit and at all subsequent study visits by pressure and joint manipulation. Joint pain/tenderness will be classified as present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA"). For DAS28 (ESR) calculation, the 28 joints assessment will be used ([Appendix F](#)).

The TJC and SJC should be performed by the clinical assessor who will be blinded to the subject's MRI and US results. It is the responsibility of the Principal Investigator to ensure all assessors are qualified to perform joint assessments. If possible, each subject should have the same assessor throughout the study as much as possible.

Physician's and Subject's Global Assessment and Assessment of Pain Sleep Disturbance by Visual Analog Scale (VAS)

VAS will be used to assess the physician's and subjects 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:

- *Physician'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

- *Subject'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 (ESR) 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

- *Subject's assessment of pain (within last week)*

The subject will rate the severity of pain from 0 to 100 (see example below):

Please place a vertical mark on the line below to indicate how much pain you have had due to rheumatoid arthritis IN THE PAST WEEK:

0 _____ 100
No Pain Severe Pain

- *Subject's assessment of sleep disturbance (within last week)*

The subject will rate the severity of sleep disturbance from 0 to 100 (see example below):⁶⁹

How much of a problem has sleep (i.e., resting at night) been for you IN THE PAST WEEK?

Please place a vertical mark on the line below that best describes how much of a problem sleep has been for you on a scale of 0 – 100.



The VAS assessments are to be performed at all study visits beginning at the dbBaseline Visit.

Morning Stiffness Assessment

Duration of morning stiffness reported by subjects as the average daily length during the past week in minutes (from time of awaking to time of maximal improvement) will be captured in the eCRF.⁷⁰

Severity of subject's morning stiffness will be assessed by a numeric rating-scale (NRS) with a 0 to 10 score range on the below self-reported questionnaire:⁷¹

- *Subject's assessment of morning stiffness severity (within last week)*

The subject will rate the severity of morning stiffness from 0 to 10 in a numeric rating-scale where 0 is "not severe" and 10 is "very severe" (see example below):

Please place an "X" in the box below to indicate how severe was your morning stiffness IN THE PAST WEEK:

0	1	2	3	4	5	6	7	8	9	10
Not Severe										Very Severe

DAS28 (CRP) and DAS28 (ESR)

The 4 variables DAS28 (ESR)^{29,72} will be completed at all designated study visits listed in [Table 1](#). The DAS28 (ESR) should be calculated using all parameters including ESR from the current visit.

The 4 variables DAS28 (ESR) calculation used for study eligibility, enrollment and monitoring will be calculated by the eCRF as below. Upon discussion with the SDP, the 3 variable DAS28 (ESR) can be used during the trial to evaluate flare if the PGA score is not available. For the purpose of chart review for study eligibility and inclusion, the 3 variable DAS28 (ESR) can be used when the Subject's Global Assessment of Disease Activity (PGA) is not available.

4 variables DAS28 (ESR):

$$\text{DAS28-ESR}(4) = 0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \text{natural logarithm} (\ln)(\text{ESR}^{\#}) + 0.014 \times \text{Global Health (GH)}^{\gg}$$

3 variables DAS28 (ESR):

$$\text{DAS28-ESR}(3) = [0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \ln(\text{ESR}^{\#})] \times 1.08 + 0.16$$

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

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

ESR refers to Erythrocyte Sedimentation Rate evaluated at the site at current visit and expressed in mm/hr (1st hour).

» GH refers to the Subject's Global Assessment of Disease Activity (PGA).

4 or 3 (if PGA is not available) variables DAS28 (CRP)²⁹ may be calculated based on patient chart review for study Screening as below:

4 variables DAS28 (CRP):

$$\text{DAS28-CRP (4)} = 0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.36 \times \ln(\text{CRP}^{\&+1}) + 0.014 \times \text{GH}^{\gg} + 0.96$$

3 variables DAS28 (CRP):

$$\text{DAS28-CRP (3)} = [0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.36 \times \ln(\text{CRP}^{\&} + 1)] \times 1.10 + 1.15$$

- * TJC28 refers to the Subject's total Tender Joint Count out of the provided 28 evaluated joints.
- ** SJC28 refers to the Subject's total Swollen Joint Count out of the provided 28 evaluated joints.
- & CRP refers to the c-reactive protein lab value. CRP unit in the DAS28 (CRP) equation is expressed as mg/L.
- » GH refers to the Subject's Global Assessment of Disease Activity (PGA).

Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)

CDAI⁷³ and SDAI^{73,74} will be completed at visits according to the scheduled in [Table 1](#). The SDAI and CDAI will be calculated as part of the statistical analysis using all parameters including CRP from the same visit (and as such calculated at the next Visit).

$$\text{SDAI} = (28\text{TJC}^*) + (28\text{SJC}^*) + \text{PhGA}^{**"} + \text{PGA}^{\ll} + \text{CRP}^{\&}$$

$$\text{CDAI} = (28\text{TJC}^*) + (28\text{SJC}^{**}) + \text{PhGA}^{"} + \text{PGA}^{***}$$

- * TJC28 refers to the Subject's total Tender Joint Count out of the provided 28 evaluated joints.
- ** SJC28 refers to the Subject's total Swollen Joint Count out of the provided 28 evaluated joints.
- " PhGA refers to Physician's global assessment of disease activity.
- & CRP refers to the c-reactive protein lab value. CRP unit in the DAS28 (CRP) equation is expressed as mg/L.
- *** PGA refers to the Subject's Global Assessment of Disease Activity (PGA).

Other Patient Reported Outcomes

Subjects will complete the following questionnaires according to the schedule in [Table 1](#):

- Health Assessment Questionnaire – Disability Index (HAQ-DI)⁷⁵ to assess the physical function and health-related quality of life of each subject ([Appendix G](#)).
- Functional Assessment of Chronic Illness Therapy-fatigue (FACIT-fatigue)⁷⁶ to assess current fatigue as it's part of the RA symptoms and frequently associated with flaring ([Appendix H](#)).
- Treatment Satisfaction Questionnaire for Medication (TSQM)⁷⁷ to assess satisfaction with current RA treatment ([Appendix I](#)).
- Work Productivity and Activity Impairment (WPAI)⁷⁸ to assess impact of RA on work productivity and non-work activity limitation ([Appendix J](#)).
- Short Form-36 Health Survey Questionnaire (SF-36),⁷⁹ a general measure to assess health and well-being ([Appendix K](#)).

Flare Severity Assessment

At the Flare Week 0 Visit, severity of flare⁸⁰ as assessed by a numeric rating-scale (NRS) with a 0 to 10 score range will be recorded:

- *Physician's assessment of Flare severity*

Physician will rate the severity of flare from 0 to 10 as follows:

0	1	2	3	4	5	6	7	8	9	10
Not Severe										Very Severe

- Subject's assessment of Flare severity
Subjects will rate the severity of their flare from 0 to 10 in a numeric rating-scale where 0 is "not severe" and 10 is "very severe" (see example below):

Please make an "X" on the box below to indicate how severe your flare is:

0	1	2	3	4	5	6	7	8	9	10
Not Severe										Very Severe

RAPID 3 at Office and In-Home Disease Assessment

Routine Assessment of Patient Index Data (RAPID-3)⁸¹ a validated disease activity score assessing physical function, patient global assessment for pain and patient global health will be completed at each scheduled visit ([Appendix L](#)).

Additionally, at the Flare Week 0 visit, subjects will be given a RAPID-3 questionnaire assessment and asked to complete the answers weekly at home without calculating the scores (and return at each visit thereafter) until Flare Week 16.

Musculoskeletal Ultrasound (US)

Investigators will, at study start indicate, state if they want to participate in the optional US assessments or not. If they decide to and the pre-requirements criteria are met (as per the Ultrasound manual), they should perform US for every subject they recruit at time points indicated by the protocol; exceptions are allowed upon discussion with Study Designated Physician. For sites participating in the ultrasound assessments, all subjects from the site should undergo the US scans and assessments as per protocol;

For the sites participating in the optional US assessment, high-end ultrasound equipment is recommended. The US must be performed by a Rheumatologist with Ultrasonography verifiable training and/or certification and at least 3 years of regular US experience; prior experience in multicenter ultrasound study(ies) is recommended, otherwise training will be provided. The Ultrasonographer must be independent of the clinical Investigator and will be blinded for subject characteristics; he/she should be the same person throughout the study, and a back-up with same qualifications should be appointed. All personnel who perform study-related US examinations must have been previously trained by the sponsor or sponsor representative as part of this study. The assessments and scoring will be

locally performed and afterwards the report of US assessments from all subjects will be sent to the central Imaging vendor. For the first subject enrolled and for the first subject with flare assessments further procedures for quality assessment are required (as per ultrasound manual). US should be done after clinical examination and prior to injecting study medication. It is recommended that subjects are in rest for around 2 hours and have not been drinking coffee or smoking (for the last 8 hours) or taking NSAIDs (for the last 12 hours) prior to the US assessment.

The optional US will be performed during the Lead-In Period or at the dbBaseline Visit prior to randomization and at Flare Week 0 Visit (when applicable and at or up to 7 days after the visit) to assess synovial hypertrophy, tenosynovitis and erosions through gray scale ultrasonography (GSUS) and synovitis/vascularization through Power Doppler Ultrasonography (PDUS).

The US assessment will consist of a systematic longitudinal and transverse multiplanar examination of 46 joints and 18 tendon/tendon compartments:

- The following bilateral joints were investigated for the presence of intra-articular B-mode synovial hypertrophy (SH) and synovial Power Doppler (PD) signal: glenohumeral (i.e., posterior and axillary recesses and biceps sheath), elbow (i.e., anterior, posterior and lateral recesses), wrist (i.e., radiocarpal, midcarpal, and distal radioulnar joints; dorsal recesses), first through fifth metacarpophalangeal (MCP) (i.e., dorsal recesses), first through fifth proximal interphalangeal (PIP) of the hands (i.e., dorsal and palmar recesses), hip (i.e., anterior recess), knee (i.e., anterior and parapatellar recesses), ankle joints (i.e., anterior, lateral, and medial recesses of tibiotalar joint; and medial and lateral recesses of subtalar joint), and second through fifth metatarsophalangeal joints (i.e., dorsal recess).
- The following bilateral tendon will be assessed for GS and Doppler tenosynovitis 2nd, 4th and 6th extensor compartments at the wrist, 2nd – 5th finger flexor tendons, tibialis posterior and peroneal tendons.

The 46-joint assessment complemented with 18 tendon compartments assessment will provide more data than the reduced scoring and potentially increase sensitivity to change and correlate with risk of flare.^{82,83}

Synovial hypertrophy (SH), synovial power Doppler (PD), GS and Doppler tenosynovitis will be defined and scored according to the Outcome Measures in Rheumatology Clinical Trails (OMERACT) as per more details provided in [Appendix N](#). Sites participating must have the qualified personnel as well as available US machines meeting the minimum requirements as described together with more detailed instructions including the scoring system in a separate US manual.

12-Lead Electrocardiogram (ECG)

If this is not available, a resting 12-lead ECG will be performed at the designated study visits in [Table 1](#). A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. Any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible Clinical Research Associate (CRA) and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 12 months of Screening, a repeat ECG at Screening will not be required, provided all protocol required documentation is available. If there are other findings that are clinically significant, the Principal Investigator must contact the Study Designated Physician before enrolling the subject. Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the Investigator.

Chest X-Ray (CXR)

All subjects will undergo a standard CXR (posterior-anterior [PA] and lateral views) at the Screening Visit to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal chest x-ray within

12 months of Screening, provided all protocol required documentation is available at the site (as outlined below).

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

In the assessment of the chest x-ray, a radiologist must note the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report.

Magnetic Resonance Imaging (MRI)

An MRI of the most affected or of the dominant hand (2nd to 5th MCP) and wrist (if both sides are considered equally affected) will be performed to all subjects during the Lead-In Period (prior to dbBaseline Visit) and the Final/Early Termination Visit (if last MRI \geq 12 weeks before).

In order to assess inflammatory as well as destructive changes in RA joints, High-field MRI with gadolinium will be performed.

A central imaging laboratory designated by AbbVie will analyze the required digital images and the OMERACT RAMRIS scoring for synovitis, erosions, BME and tenosynovitis will be calculated.

MRI assessors will be blinded for subject characteristics and the clinical assessors will be blinded for MRI scores in order to maintain the independence of the results and allow for an association analysis.

Procedures for MRI requirements, sequences and digital imaging processing to the vendor will be provided in a separate manual and in [Appendix M](#).

TB Screening

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or a Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

Subjects that have a negative PPD or IGRA test and are considered at risk for having latent TB (any immunosuppressed patient with a strong suspicion of TB exposure and no prior vaccination with Bacille Calmette-Guérin) need to be evaluated by a TB expert before Week 0.

Subjects at risk for TB exposure are defined as:

- subjects that have household contact with a person with active TB
- subjects living in areas with high incidence of TB
- subjects that frequently visits areas with high prevalence of active TB

If a subject had a negative PPD or IGRA test within 12 months prior to Screening, and all protocol required documentation is available, this test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases must be discussed with the AbbVie Study Designated Physician.

For the PPD test:

The subject will be required to have the PPD test read by a licensed healthcare professional 48 to 72 hours (or according to manufacturer's guide) after placement when the induration is maximal. An induration (not erythema) of 5 mm or greater will be considered as PPD positive, irrespective of BCG status or local guidelines. The induration must be recorded in mm not as positive or negative. The absence of induration should be recorded as "0 mm," not "negative."

Subjects who have had an ulcerating reaction to a PPD skin test in the past should not be re-exposed and should not be tested at Screening but will be considered PPD positive.

If there are sites where the accepted testing materials are not available an alternative may be substituted, but the method must be submitted and approved by AbbVie prior to use with study subjects.

In the assessment of the chest x-ray, a radiologist must note the presence or absence of 1) calcified granulomas, 2) pleural scarring/thickening, and 3) signs of active TB. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator must contact the AbbVie Study Designated Physician before enrolling the subject.

If the PPD or the IGRA test is positive or the subject has a CXR or TB expert opinion indicative of latent TB, the subject will be required to initiate and have taken at least 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of the United States Center for Disease Control (CDC) and Prevention recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy.

Subjects with a prior history of latent TB that have a documented completion of the CDC recommended or local guideline recommended prophylaxis may be permitted to enroll. If the subject has a prior history of latent TB but has not completed or received prophylaxis, prophylaxis must be initiated. The prophylactic treatment must be maintained during the study until its recommended full course is completed.

If the subject has a prior history of active TB they must have documentation of completion of CDC recommended or local guideline recommended treatment and documentation of resolution of the infection.

In the event both a PPD test and an IGRA test are performed, the result of the IGRA test will supersede the result of the PPD test. If the IGRA test is indeterminate, the site should repeat the test with another blood sample or perform a PPD test. If the second IGRA test is also indeterminate, the subject is considered to be positive and should initiate TB prophylaxis.

Newly initiated prophylactic treatment should be captured on the concomitant medications page in the eCRF and in the source documents. Prior therapy should be captured in medical history.

Annual TB Testing:

For subjects with a negative TB test at Screening (or within the last 12 months of Screening), either an annual PPD or IGRA test will be required for any subject participating in the trial 52 weeks after their last TB test (\pm 2 months). If the annual TB screen is positive (PPD is positive or the IGRA test is positive), a CXR may be required for evaluation of active TB. For any subject with a positive annual TB screen, the site should contact the AbbVie Study Designated Physician for further discussion. Subjects found to have latent TB, will be required to start a course of CDC recommended prophylaxis or prophylaxis per local guidelines as soon as possible. Any positive TB screen after the subject has started the study, should be reported as an AE.

An annual TB screen with PPD or IGRA testing will not be required for subjects who have been treated for latent or active TB or have had a positive TB test (PPD or IGRA) at any time (prior to the study, Screening, annual evaluation, or testing performed at any time point during the study). For such subjects, annual evaluation by a physician for clinical signs/symptoms of active TB (including a directed TB history and physical exam including lungs, lymph nodes and skin) or newly identified TB risk factors will be required 52 weeks after the previous TB test. For any subject with clinical signs/symptoms of active TB or newly identified TB risk factors, a CXR may be required for evaluation of active TB, and it is recommended to contact the Study Designated Physician for further guidance.

Hepatitis B Testing

If a subject had a negative hepatitis B virus (HBV) result within 12 months prior to Screening and all protocol required documentation is available, these tests repetition are not required. At screening subjects must be assessed for high risk of exposure to hepatitis B since their last test. If high risk is suspected, a hepatitis B test should be performed.

If not or no proper documentation is available all the following procedures are requested:

- Subjects will be tested for the presence of HBV at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab). If test results are positive for HBc Ab or HBs Ab, HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

Pregnancy Tests

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. At the Week 0 Visit, subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. Investigators may conduct more frequent urine pregnancy testing as necessary according to their judgment. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

All women of childbearing potential will have a repeat urine pregnancy test at the Final Study Visit performed locally by designated study personnel.

Laboratory Tests

Blood and urine samples will be obtained for clinical laboratory tests. Samples will be obtained at the designated study visits in [Table 1](#). Samples will be obtained for the laboratory tests listed in [Table 2](#).

When blood draws are performed as part of a clinic visit, the draws should be performed after completion of questionnaires and vital sign measurements, and before study drug administration. Urine samples will be obtained for macroscopic urinalysis (dipstick done at the central laboratory which will include specific gravity, pH, protein, glucose, ketones, blood and nitrites) and a microscopic urinalysis at Screening. For all other visits that require a urinalysis, the central laboratory will perform a urine dipstick analysis and if the results are abnormal, the central laboratory will perform a microscopic urinalysis.

If needed, according to previous sections, blood samples for hepatitis B will be obtained at Screening Visit only. A subject will not be eligible for study participation if test results indicate chronic or current hepatitis B infection.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipment of appropriate samples.

The laboratory results will be provided by the central laboratory to the investigative site where they will be reviewed, signed and dated by the Investigator and filed as source data. For any abnormal value outside of the reference range, the Investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). All abnormal laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol (total, HDL, LDL) Total protein Glucose Triglycerides	Specific gravity Ketones pH Protein Glucose Leukocytes Nitrite Blood	ESR CRP RF Immunoglobulin M (IgM) ACPA ANA Anti dsDNA Serum pregnancy (Human Chorionic Gonadotropin [bHCG]) testing Hepatitis B surface antigen (if applicable) Quantiferon-TB Gold (if applicable)
			Biomarkers
			Matrix metalloproteinase 3 (MMP-3) Type I Collagen neo-epitope (C1M) Type III collagen neo-epitope (C3M) Matrix metalloproteinase mediated c-reactive protein (CRPM) Matrix metalloproteinase- degraded citrullinated vimentin (VICM) Serum amyloid-associated protein (SAA) Interleucin-6 (IL-6) Chemokine (C-X-C motif) ligand 10 (CXCL-10) Chemokine (C-X-C motif) ligand 13 (CXCL-13) Pharmacogenetic DNA/mRNA (Optional) Additional biomarkers (Optional)

Biomarker Laboratory Assessments

Samples will be obtained for biomarker analysis at the designated study visits in [Table 1](#): dbBaseline, Week 10, 16, 28, 40, Early Termination Visit, and (if applicable) at Flare Weeks 0, 4 and 16 and as described in more detail under Section [5.3.3](#). The samples collected will be used to evaluate the following biomarkers:

- MMP-3, C1M, C3M, CRPM, VICM, SAA, IL-6, CXCL-10, CXCL-13

At the time of analysis, other potential biomarkers identified as adding value to predict flare in this patient population may be included.

At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for samples to be stored for possible future research of new biomarkers.

Serum Adalimumab Concentrations

Samples will be obtained for serum adalimumab concentrations at the designated study visits in [Table 1](#) and described in more detail under Section [5.3.2](#).

Anti-Adalimumab Antibodies

Samples will be obtained for anti-adalimumab antibodies at the designated study visits in [Table 1](#) and described in more detail under Section [5.3.2](#).

Pharmacogenetic Sample

Samples will be obtained for pharmacogenetic analysis (DNA/mRNA) at the designated study visits in [Table 1](#) and described in more detail under Section [5.3.4](#).

Adverse Events

Adverse events will be assessed at every study visit from the first dose of study drug at Week 0 Lead-In through the Final/Early Termination Visit, and during the 70-day phone call or clinic visit (if applicable). Subjects may discontinue adalimumab treatment at any

time during study participation. Subjects that end study participation early will have an Early Termination/Final Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events. Refer to Section 6.1.4 for additional information.

Prior and Concomitant Therapy Assessment

Any medication that the subject is receiving at the time of Screening or receives during the study must be recorded on the source documents as well as the appropriate eCRF. Previous prescription medications or physician-administered treatments used for RA prior to study entry will be recorded. See Section 5.2.3 for full details regarding documentation of prior and concomitant therapy.

Enrollment

The subject will not be assigned a screening number for this study. Subject numbers will be centrally assigned by the Interactive Response Technology (IRT), in consecutive order at each site at Screening. Each subject will be assigned a unique subject number.

Subjects who meet the inclusion criteria for the Lead-In Period and do not meet any of the exclusion criteria will be enrolled in the 4-week Lead-In Period.

Upon confirmation of inclusion criteria including DAS (ESR) < 2.6, all Screening laboratory results must be reviewed, signed and dated by the Principal Investigator prior to the Lead-In Day 1 visit. Subjects will not be enrolled into the Lead-In Day 1 period of the study if laboratory or other Screening results abnormalities are deemed clinically significant by the Principal Investigator.

Randomization

Upon confirmation of the DAS requirements, subjects will be randomized to receive either adalimumab 40 mg subcutaneous (SC) at the dbBaseline Visit (Arm 1) followed by dosing every 3 weeks until flare or matching placebo (Arm 2) in a 5:1 ratio double-blind fashion to the treatment groups.

Dispense Study Drug

Adalimumab during the Lead-In Period and Open-Label Rescue Arm as well as adalimumab/placebo study drug during the Double-Blind Period will be administered to subjects by study site medical staff, by him/herself or by a designee (friend, family member or health care professional) throughout the study in accordance with [Appendix C](#).

Once the limit of 20% of enrolled subjects on other csDMARDs or no csDMARDs is met, only subjects on concomitant methotrexate will be allowed into the trial.

Subjects or a designated family member or friend will be trained to administer study medication, if needed or considered appropriate, during the first visit or several times. This training must be documented in the subject's source document.

Subjects or a trained designated family member or friend or a health care professional will administer the injections of the study medication in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

Subjects will maintain a Subject Dosing Diary for all study medication administered outside of the study visit (i.e., at home). The Subject Dosing Diary will be reviewed and verified for compliance at each clinic visit. All relevant dosing information will be retained by study personnel. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately. A sample of the Subject Dosing Diary is presented in [Appendix D](#).

For subjects that cannot/will not self-administer study drug or do not have adequate support (friend, family member or healthcare professional) at home, administration will occur in the clinic.

At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. If an anaphylactic reaction or other serious allergic reaction occurs, administration of study medication should be discontinued immediately and appropriate therapy initiated. When dosing at home,

subjects should be instructed to contact the site immediately with any signs or symptoms of a reaction.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the original dosing schedule as soon as possible.

The subject must be instructed to return study drug at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.7.

5.3.2 Drug Concentration Measurements

Blood samples for the pharmacokinetic (PK) measurement of serum adalimumab levels and anti-adalimumab antibody (AAA) concentrations will be taken at the following visits, as specified in [Table 1](#):

- Blood samples will be collected at dbBaseline, Weeks 10, 16, 28, 40/Early Termination Visit.
- Subjects who flare will have blood samples collected at the Flare Weeks 0, 4, 10 and 16.

Collection of Samples for Serum Adalimumab Concentration and AAA Analysis

Blood samples for serum adalimumab concentration and AAA will be collected prior to dosing by venipuncture into appropriately labeled 4 mL evacuated serum collection tubes without gel separator. Sufficient blood will be collected to provide approximately 2 mL serum for the adalimumab assay. The central laboratory will provide supplies for sample collection, processing, storage and shipment. Please refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipment. Additional PK/AAA assays may be analyzed (where allowed by local guidelines).

5.3.3 Biomarker Measurements

Blood samples for biomarker analysis will be collected at dbBaseline, Weeks 10, 16, 28 and 40/Early Termination. Subjects who flare will have blood samples collected at Flare Weeks 0, 4 and 16.

Collection of Samples for Biomarker Measurements

Blood samples for biomarker analysis will be collected by venipuncture into an appropriately labeled 6 mL evacuated serum collection tube without gel separator. Sufficient blood will be collected to yield approximately 2.4 mL of serum for each sample.

In addition, at the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for the following samples to be collected and stored for possible future research:

A blood sample will be collected by venipuncture into an appropriately labeled 6 mL evacuated serum collection tube without gel separator. Sufficient blood will be collected to yield approximately 2.4 mL of serum for each sample.

5.3.4 Pharmacogenetic Measurements

Blood samples for the optional pharmacogenetic (PG) measurement will be taken at the following visits, as specified in Table 1: Blood samples for the optional analysis of DNA are collected at dbBaseline and Final/Early Termination Visit.

Blood samples for the optional analysis of RNA is collected at dbBaseline, Weeks 10, 16, 28, 40/Early Termination. Subjects who flare will have optional blood samples collected at Flare Weeks 0, 4 and 16.

Collection of Samples for Pharmacogenetic Measurements

For each subject who consents to provide samples for pharmacogenetic analysis:

- One 3 mL whole blood sample for DNA isolation will be collected. The sample collection tube will minimally be labeled with "PG-DNA," protocol number, subject number and the study visit.
- Two 2.5 mL whole blood samples for mRNA isolation. The sample collection tubes will be labeled with "PG-mRNA" or "BB-RNA," protocol number, subject number and study visit.

The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

5.3.4.1 Handling/Processing of Samples

The blood samples for adalimumab, AAA and biomarkers will be handled/processed as outlined below. At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research. Subjects will be able to decline storing samples for possible future research during the consenting process discussed further in Section 9.3.

5.3.4.1.1 Serum Adalimumab Concentration and AAA Analysis

The blood samples for adalimumab and AAA will be centrifuged within 30 – 60 minutes of collection using a centrifuge to separate the serum and should be documented in the source document. Serum samples will be split into two aliquots, both being shipped to the central laboratory. Split-2 aliquots should not be shipped with the split-1 aliquots from the same draw. The serum samples will be transferred using plastic pipettes into screw capped polypropylene tubes provided by AbbVie and labeled with the drug name, type of sample (serum [SRM]), the protocol number, the subject number, the planned study day, and the assay type (PK Split1, PK Split2, AAA Split1, AAA Split2). Serum samples will be frozen within 2 hours after collection and will remain frozen at –20°C or colder until shipped and should be documented in the source document. Sites that do not have access to a –20°C or colder freezer will need to ship the samples the day they are collected.

Additional detailed instructions for the handling and processing of samples will be provided from the central laboratory.

5.3.4.1.2 Biomarker Analysis

The central laboratory will provide the supplies for all biomarker sample collection, processing, storage and shipment. Please refer to the central laboratory manual for specific instructions on biomarker sample collection, processing, storage and shipment.

Biomarker samples for possible future research will be collected from subjects who consent and stored frozen for exploratory analysis of non-genetic biomarkers related to the subject's disease, related conditions and/or response to study drug, in terms of tolerability and safety. These samples may also be used for the development of diagnostic tests related to the disease. Results of exploratory analyses, if any, will not be reported with the study summary. AbbVie will store the samples in their Immunology Biobank, which is a secure storage space, with adequate measures to protect confidentiality. The samples will be retained for no longer than 20 years after completion of the study (where allowed by local guidelines). The samples will only be used for the purposes described here and in the informed consent.

5.3.4.1.3 Pharmacogenetic Analysis

Samples (DNA/mRNA) will be shipped frozen to AbbVie or a designated laboratory for long-term storage. The DNA and mRNA samples will be stored in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on adalimumab (or drugs of this class) continues but no longer than 20 years.

Instructions for the preparation and shipment of pharmacogenetic samples will be provided in the laboratory manual.

5.3.4.2 Disposition of Samples

The frozen blood samples will be packed in dry ice sufficient to last 3 days during transport and shipped from the study site to central laboratory according to instructions

from the central laboratory manual. An inventory of the samples included will accompany the package. The central laboratory will then ship the samples to AbbVie for analysis.

5.3.4.3 Measurement Methods

Serum concentrations of adalimumab, AAA and biomarkers will be determined using validated ligand binding methods under the supervision of the Drug Analysis Department at AbbVie.

5.3.5 Efficacy Variables

5.3.5.1 Primary Efficacy Variables

The primary explanatory variables are the Baseline hand and wrist synovitis and bone marrow edema (BME) RAMRIS scores as well as a composite of both; the dependent variable is the occurrence of flare up to Week 40 in the tapering arm.

5.3.5.2 Secondary Variables

Secondary Variables Include the Following:

- Time to flare
- Flare severity
- Proportion of subjects with a flare
- Subject demographics and clinical disease characteristics at dbBaseline, including:
 - Smoking status, co-morbidities, anti-citrullinated peptide antibody (ACPA) status, Rheumatoid Factor (RF) status, disease duration, previous treatment with csDMARDs or bDMARDs or both, duration of adalimumab therapy, remission duration, disease activity, CRP and HAQ
- Proportion of subjects who regain clinical remission (defined as DAS28 [ESR] < 2.6 or defined as DAS28 [ESR] decrease > 1.2 if DAS28 [ESR] was less than 2.6 at flare) in the Open-Label Rescue Arm over time
- Time to regain clinical remission in the Open-Label Rescue Arm

- Proportion of subjects with low disease activity (defined as DAS28 [ESR] < 3.2) in the Open-Label Rescue Arm over time
- Change from dbBaseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI)
- Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI [DAS28 (ESR) < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8]) throughout the study
- Change from Baseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores
- Change from dbBaseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) over time
- Proportion of subjects with HAQ-DI normal (HAQ-DI ≤ 0.5) at dbBaseline and at Week 40
- Change from dbBaseline in RAPID 3 scores assessed during Visits
- Change from Flare Week 0 in RAPID 3 at home assessments
- Change from dbBaseline in Swollen Joint Count (both 28 and 66 joints)
- Change from dbBaseline in Tender Joint Count (both 28 and 68 joints)
- Change from dbBaseline in Patient's Global Assessment of Disease activity
- Change from dbBaseline in Patient's Global Assessment of RA pain
- Change from dbBaseline in Physician's Global Assessment of Disease activity
- Change from dbBaseline in morning stiffness assessment
- Change from dbBaseline in Sleep disturbance assessment
- Change from dbBaseline in Treatment Satisfaction Questionnaire for Medication (TSQM)
- Change from dbBaseline in Work Productivity and Activity Impairment (WPAI)
- Change from dbBaseline in Short Form-36
- Change from dbBaseline in Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-fatigue)
- Change from dbBaseline in CRP
- Change from dbBaseline in ESR

5.3.5.3 Exploratory Variables

Exploratory Assessments Include:

- dbBaseline and change from dbBaseline to the time of flare in PDUS and GSUS individual and composite scores of synovitis, synovial hypertrophy and tenosynovitis
- dbBaseline and change from dbBaseline on biomarker values (MMP-3, SAA, C1M, C3M, CRPM, VICM, IL-6, CXCL10, CXCL13)

5.3.5.4 Pharmacokinetic Variables

Blood samples will be collected for the measurement of serum adalimumab concentrations prior to dosing at dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4, 10 and 16 (if applicable). Blood samples will be collected for the measurement of AAA at dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4, 10 and 16 (if applicable).

5.3.5.5 Pharmacogenetic Variables

DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or subject's response to adalimumab, other study treatment, in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, other genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis.

Essentially all mRNAs present in the collected peripheral blood samples may be sequenced or measured using microarray and polymerase chain reaction (PCR) techniques. The mRNA sub-study may be analyzed for RNA expression levels contributing to the subject's response to the disease or study treatment, in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Messenger RNA

analysis will be limited to studying response to disease or adalimumab therapy; no other analyses will be performed.

The samples (DNA/mRNA) may be analyzed as part of a multi-study assessment of genetic factors involved in the response to adalimumab, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to the disease. The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.6 Safety Variables

Screening assessments will include medical history, vital signs, physical examination, and clinical laboratory tests. The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, physical examination (if required) and laboratory tests.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time. 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 one of the following occurs:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Study Designated Physician.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk

as determined by the AbbVie Study Designated Physician (Section 5.2 and Section 7.0).

- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Study Designated Physician.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- Subject has dysplasia of the gastrointestinal tract or a 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.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie Study Designated Physician.

If, during the course of study drug administration, the subject prematurely discontinues study drug use, the procedures outlined for the Termination Visit must be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. If subjects discontinue the study during the lead-in observational period, prior to randomization, a short Early Termination visit is required for: returning study material and drug, assess any safety/adverse events, collect reason for discontinuation and a 70-day follow-up call/visit; the remainder of full Early Termination Visit study procedures can be completed per the investigator's discretion. 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 phone call will be made to all subjects approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last dose of study drug 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.

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

For subjects entering the 4-week Lead-In Period, OL adalimumab 40 mg eow will be provided. Drug will be sc self-administered every other week at approximately the same time of the day.

Starting at the dbBaseline visit, subjects who are eligible for randomization will receive the first dose of blinded drug: adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. Drug will be subcutaneously administered as a 40 mg or placebo dose every 3 weeks at approximately the same time of day.

Subjects who meet flare criteria will be entering an Open-Label Rescue Arm and OL adalimumab 40 mg will be administered every other week for 16 weeks.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in [Table 3](#).

Table 3. Identity of Investigational Products

Drug	Dosage Form	Device	Formulation	Manufacturer
Adalimumab	Parenteral	Pre-filled syringe	40 mg/0.8 mL solution for injection Adalimumab/Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie
Placebo for adalimumab	Parenteral	Pre-filled syringe	0.8 mL solution for injection Mannitol, Citric acid monohydrate, Sodium citrate, Disodium phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, Sodium chloride, Polysorbate 80, Water for injections, Sodium hydroxide added as necessary to adjust pH	AbbVie

5.5.2.1 Packaging and Labeling

Investigational product will be packaged separately in 0.8 mL syringe containing either adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. Each dosing kit carton will contain a pre-filled syringe to accommodate study design. The syringe and/or carton labels will minimally contain the information as required per country requirements.

All labels must remain affixed to study medication at all times, and should never be removed for any reason.

Detailed instructions and training for the administration of study drug supplies are provided in [Appendix C](#).

5.5.2.2 Storage and Disposition of Study Drug

Adalimumab/placebo pre-filled syringes are to be stored protected from light at 2° to 8°C/36° to 46°F. Study medication drug **must not be frozen at any time**. A storage temperature log is to be maintained to document proper storage conditions. The refrigerator temperature must be recorded on a temperature log to record proper function. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study medication should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) deems the medication as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

Investigational products are for investigational use only and are to be used only within the context of this study.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. Subjects who meet the inclusion and none of the exclusion criteria in Section 5.2.1 and Section 5.2.1 will proceed to enter the study Lead-In Period and double-blind randomized period. All subjects who enter the randomized period of the study will be centrally randomized at dbBaseline in a 5:1 ratio double-blind fashion using the IRT which will assign a randomization number and a treatment group according to the randomization scheme generated by AbbVie before the start of the study. The treatment group assignment will be maintained by the IRT and not provided to the site, as the subject will be referred to by the subject number assigned at Screening. The sites will be provided with appropriate kit number(s) for drug-dispensing purpose for each subject by the IRT. Study drug will be dispensed at the study visits summarized in Table 1.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1 Treatments Administered.

If a subject should forget to administer the injection of study medication on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day of their next scheduled dose. The subject should not administer two doses on the same day.

In the event the incorrect dose is taken or a dose is missed, the subject should be instructed to contact the site to determine how to proceed with dosing. The subject must record all dosing information on the Subject-Dosing Diary Sheet.

Doses not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source. The extra dose should be returned to the study site full. The subject should resume their regular dosing schedule based on the first dosing date at dbBaseline.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) the Investigator, study site personnel and the subject will remain blinded to each subject's treatment throughout the Double-Blind Period of the study. The IRT will provide access to blinded subject treatment information in the case of medical emergency.

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie Study Designated Physician (Section 7.0) prior to breaking the blind as long as it does not compromise subject safety. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drug only for use by subjects enrolled in the study.

The subject or their qualified designee will administer all doses of study drug. Appropriate site staff will supervise the subject's administration of the study drug at required in-office study visits to ensure proper injection technique. In order to document compliance with the treatment regimen, the subject will be given a dosing sheet ([Appendix D](#)) to record all injection dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication. If the subject does not return the dosing sheet, IP boxes and sharp containers (when applicable), 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 sheet is returned before completing on the applicable eCRF page.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact, at the appropriate temperature (temperature recording devices [temptales] are provided in the shipments), and in the correct amounts. This will be accomplished by documenting the condition of the shipment, verifying the kit numbers in the package against the Proof of Receipt (POR) or similar document included with each drug shipment, and documenting this verification by signing and dating the POR or similar document. The original POR Note or similar document will be kept in the site files as a record of what was received.

In addition, an accurate running inventory of study drug will be kept by the site on a Site Drug Accountability log including date received, the lot number, kit number(s), date dispensed, subject number, and the identification with date of the person dispensing the drug.

All empty IP boxes and used pre-filled syringes will be inventoried by the site. Each subject will be given their own sharps disposal container to store used pre-filled syringes. Empty IP boxes and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Empty Boxes and returned Sharps containers will be retained (unless prohibited by local law) until the CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via study medication logs, source documents, subject dosing sheets, empty IP boxes and by visually inspecting the syringes in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used pre-filled syringes have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the destruction methodology should be maintained at the site's facility. After drug accountability has been completed at the site, unused medication will be destroyed on site according to local procedures or regulation or returned to a destruction facility by the CRA.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This Phase 4 study is designed to investigate the association between residual disease activity at baseline, and the occurrence of flares in RA patients on adalimumab who are in sustained clinical remission (DAS28 [ESR] < 2.6) and submitted to an adalimumab dose tapering regimen or withdrawal. The randomization 5:1 including a control arm of withdrawal of adalimumab is introduced as a study design element to ensure the objectivity of flares assessments in the primary study arm. For subjects who flare the Open-Label Rescue Arm will provide evidence on the effect of re-treatment with adalimumab eow. The proposed sample size and 36-week duration of the Double-Blind Period is based on the estimated risk (of approximately 30%) and time to the occurrence of flare in subjects with established RA in clinical remission upon tapering or withdrawing TNFi therapy.^{20-22,24}

5.6.2 Appropriateness of Measurements

Standard statistical, clinical and laboratory procedures will be utilized in this study. Efficacy measurements in this study have been selected to assess disease activity and the occurrence of flares in subjects with RA using clinical scores that are standard and generally accepted. Imaging techniques with MRI and US identifying subclinical inflammation (synovitis, etc.) have been correlated with risk of disease progression and flaring in RA patients otherwise in clinical remission. Thus, assessing their association with occurrence of flaring (versus non-flaring) in a dose tapering or withdrawal treatment strategy is deemed appropriate. The biomarker, PK analysis and the investigation of their correlation with patient outcomes is exploratory but relevant to gather more potential individual predictors for the clinical outcomes of tapering or withdrawal of adalimumab.

5.6.3 Suitability of Subject Population

Subjects age ≥ 18 years diagnosed with RA, on a stable dose of adalimumab 40 mg sc eow (for ≥ 12 months prior to Screening Visit) in combination with methotrexate (MTX; at stable dose for ≥ 12 weeks prior to the Screening Visit) or if not on MTX in a stable other allowed csDMARD or no csDMARD regimen for ≥ 12 weeks prior to Week 0 Visit) and in documented clinical remission (DAS28 [ESR] < 2.6 or DAS28 [CRP] 2.6) for ≥ 6 months prior to the study are eligible for this study. Patients who are not on stable concomitant MTX will be allowed as per current clinical practice, but limited to 20% of the study population. This is the target population that in routine clinical practice is, in general, being considered for therapy tapering strategies. The recently updated EULAR recommendations for the management of patients with RA¹¹ provide some orientation to this extent but do not contain specific guidance to characterize the patients that could actually be submitted to a tapering regimen and do highlight this as an area of research interest.

5.6.4 Selection of Doses in the Study

The recommended dose of adalimumab for adults with RA is 40 mg administered eow. Adalimumab 40 mg eow has demonstrated to improve clinical, function and to halt radiographic progression of RA for up to 10 years of treatment.¹⁰

Dose tapering strategies with adalimumab are starting with a prolongation of injection intervals to every 3 weeks.^{11,24,26,65-68} Thus the selection of patients suitable for drug tapering should be based on the clinical course of this initial dose tapering regimen.

In previous studies, a dose tapering strategy with increasing the interval of administration of adalimumab to every 3 weeks followed by withdrawal when possible has been tolerated by a significant proportion of patients.^{24,65-68} In this study, subjects who experience a flare at any time will initiate OL adalimumab 40 mg eow rescue therapy and will be allowed to add other treatments at the Investigator's discretion.

6.0 Complaints

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

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.1.5). For adverse events, please refer to Sections 6.1 through 6.1.7. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of 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.

6.1.1 Definitions

6.1.1.1 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 6.1.7 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.

6.1.1.2 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.
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For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 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	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
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No Reasonable Possibility An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

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

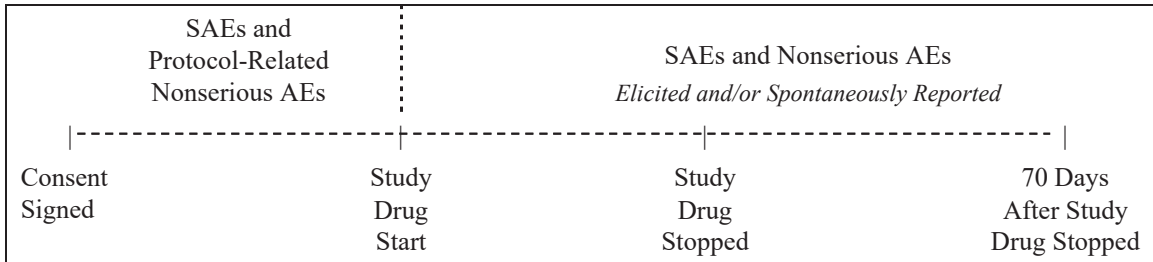
If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 70 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent. Adverse event information will be collected and recorded on the appropriate eCRFs.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination/Final Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events. 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.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the physician will notify the AbbVie Clinical Pharmacovigilance Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the Rave EDC system should be documented on the SAE Non-CRF Forms and sent to the Clinical Pharmacovigilance Team within 24 hours of being made aware of the adverse event.

FAX to: [REDACTED]
Email to: [REDACTED]

For safety concerns, contact the Immunology Safety Team at:

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

Office: [REDACTED]
 Email: [REDACTED]

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

Primary Study Designated Physician:



Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: 

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

6.1.6 Pregnancy

Pregnancy in a study subject or a partner of a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1). Pregnancies in study subjects and their partners will be collected from the date of the first dose through 150 days following the last dose of study drug.

Information regarding a pregnancy occurrence in a study subject or a study subject's partner and the outcome of the pregnancy will be collected. In the event of pregnancy

occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to the collection of any such information.

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

6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with adalimumab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (see Section 6.0 for definitions). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to use, every attempt should be made to contact the AbbVie Study Physician for direction on re-introduction of adalimumab therapy after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

6.2 Product Complaint

6.2.1 Definition

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

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, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

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

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device 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 (syringe). 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) 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 CRO Clinical Monitor or the following AbbVie Clinical Monitors:

Primary Contact:

Alternate Contact:



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

For the purposes of this protocol, reportable deviations are defined as:

- 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 Analysis Population

The analysis population for both efficacy and safety assessment is All Treated Subjects. It includes all subjects who have received at least one dose of double-blind study medication.

Unless otherwise specified, efficacy and other assessment will be primarily analyzed for subjects who are randomized to the adalimumab 40 mg q3 weeks arm (taper arm) and have received at least one dose of study medication. Descriptive statistics will be provided for the subjects who are randomized to the placebo arm (withdrawal arm) and have received at least one dose of study medication.

In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary efficacy assessment may be conducted on the per protocol population, which consists of all treated subjects who complete the study or otherwise have had a flare and are not major protocol violators.

8.1.2 Planned Methods of Statistical Analysis

Complete and specific details of the final statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The analysis will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

Unless otherwise stated, all statistical inference will be based on a 2-sided alpha-level of 0.1. No multiplicity adjustment will be conducted. Descriptive statistics include the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables; and counts and percentages for discrete variables.

8.1.3 Analysis of Demographic Data and Double-Blind Baseline Disease Characteristics and Other Analyses

Demographic and double-blind Baseline characteristics for all randomized subjects will be summarized by treatment arm and descriptive statistics will be provided.

Medical history will be presented by count and percentage of subjects broken down by Body system and Diagnosis. Prior and concomitant medication will also be summarized.

Treatment duration regardless of whether rescue therapy is received will be summarized for All Treated Subjects.

8.1.4 Efficacy Analysis

8.1.4.1 Analysis for Primary Objective

The primary objective is to investigate the association between Baseline hand and wrist synovitis and BME RAMRIS scores as well as a composite of both, and the occurrence of flares up to Week 40 in the tapering arm. This association will be examined using logistic regression, which is deemed as the main analysis for the primary assessment. The 90% confidence interval of the odds ratio will be calculated. The 95% confidence intervals of the odds ratio will also be provided as an addition.

Additional analyses will be performed to assess this association using various statistical methods. Specifically, descriptive statistics of Baseline MRI composite scores (RAMRIS) scores will be provided for the two groups of subjects who flare and who do not flare, and the between-group difference in the mean scores will be computed together with a 90% confidence interval. Linear regression will be used to model the relationship between the DAS28 (ESR) at flaring (or at the end of the study for subjects who do not flare) and the Baseline MRI RAMRIS scores. Receiver operating characteristic (ROC) curve approach will also be utilized to investigate the potential flare prediction criteria based on MRI RAMRIS scores. All model based analyses may adjust for dbBaseline clinical patient characteristics including age, disease duration, previous and concomitant

treatment (such as use of MTX, use of csDMARD as versus TNFi monotherapy), etc., when appropriate.

Similar analysis will be conducted for RAMRIS synovitis scores, BME scores and the composite of both.

For subjects who prematurely discontinue in the double-blinded period (i.e., prematurely discontinue prior to the detection of flaring), their last DAS28 (ESR) score will be used to impute their flare status. All subjects who are classified as receiving rescue therapy will be treated as flare subjects.

8.1.4.2 Analysis for Secondary Objectives

To characterize the development of flares, the proportion of subjects who flare in the taper arm and withdraw arm and overall, and the 90% confidence interval of this proportion will be calculated. Time to flare in these two arms will be summarized using Kaplan-Meier survival techniques. The proportion of subjects within each level of flare severity will also be computed for the taper arm and withdraw arm and overall, accompanied by a 90% confidence interval.

To investigate the association between the occurrence of a flare and the specified dbBaseline parameters similar analyses will be conducted as for the primary assessment.

To evaluate the effectiveness of re-treatment with adalimumab 40 mg eow as a rescue therapy after flaring, the proportion of flared subjects who regain clinical remission will be calculated with a 90% confidence interval, separately for subjects from the tapering arm and from the withdrawal arms. To assess the time to regain clinical remission, the proportion of flared subjects who regain clinical remission will be summarized over time by the duration of rescue therapy, separated for subjects from the tapering arm and from the withdraw arm.

To describe the MRI change for subjects in the taper, withdraw and Open-Label Rescue Arms, the change from Baseline to end of study in MRI RAMRIS scores and its

individual component scores for synovitis and edema will be summarized separately for flared and non-flared subjects originated in the taper and withdraw arm respectively.

To describe the disease course of subjects in the taper, withdraw and Open-Label Rescue Arms, different clinical and health reported outcome measures, which are listed in Section 5.3.5.2 will be summarized over time separately for flared and non-flared subjects originated in the taper and withdraw arm respectively.

8.1.4.3 Analysis for Exploratory Objectives

The ultrasonographic assessments will be performed at dbBaseline and at flare. Descriptive statistics of ultrasonography (US) synovial inflammation (Power Doppler [PD]) and synovial hypertrophy (Gray Scale [GS]) scores at dbBaseline will be summarized for the flared and non-flared subjects to assess their association with the occurrence of RA flares. In addition, the scores at flare as well as change from dbBaseline will be summarized. Additional analyses to assess the association between dbBaseline ultrasonographic scores and the occurrence of a flare will be performed if deemed necessary.

To assess the association between dbBaseline US synovial inflammation (PD) and synovial hypertrophy (GS) scores and Baseline MRI synovitis RAMRIS score, linear regression approach will be used to modeling the relationship between the dbBaseline PDUS and GSUS scores and Baseline MRI synovitis RAMRIS score.

Biomarker values including dbBaseline and their change from dbBaseline over time will be summarized for the flared subjects and the non-flared subjects. Additional analyses to assess the association between biomarker and the occurrence of a flare will be performed if deemed necessary.

The occurrence and time to flare from dbBaseline in the concomitant MTX, other csDMARDs and no csDMARDs patients will be analyzed for potential differential effect.

8.1.5 Pharmacokinetic Analyses

Adalimumab serum concentrations will be summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non-missing observations (n_{nmis}), mean, median, standard deviation, coefficient of variation (CV), minimum, and maximum as appropriate. Individual subject concentrations versus time plots and mean concentration versus time plots by treatment group will be provided. Data listings will be generated for individual subjects. For the calculation of summary statistics and plots, concentration values below limit of quantification (LOQ) will be set to zero.

The association between dbBaseline adalimumab trough concentrations and the occurrence of flares will be assessed as appropriate. In addition, pharmacokinetic model based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

AAA will be evaluated for each subject and each study arm, and rates of AAA positive subjects will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated.

8.1.6 Safety Analysis

Treatment-emergent adverse events (AEs) will be summarized and reported. Treatment-emergent AEs are defined as AEs that begin either on or after the first dose of the study medication, through the end of the AE collection period as defined by the protocol. The number and percent of subjects experiencing treatment-emergent AEs will be tabulated by treatment and by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA[®]) preferred term. In addition, summary of treatment-emergent AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, or lead to premature study drug discontinuation will be listed and described in detail.

Mean change in laboratories variable and vital signs variables at each visit will be summarized for all treated subjects. The last evaluation prior to the first dose of double-blinded study drug will be used as dbBaseline for all analyses. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 3 or higher will be provided. Shift tables for changes from dbBaseline according to the normal range will also be provided for lab variables.

8.1.7 Interim Analysis for Double-Blind Baseline Characteristics

There are few data describing patient disease characteristics including markers of residual inflammation such as sensitive imaging assessments and potential biomarkers as well as drug levels in RA patients who are in sustained clinical remission on a stable treatment with a TNFi and MTX and/or with other csDMARDs(s) or in TNFi monotherapy. An interim analysis will be conducted to describe the dbBaseline characteristics of the RA population. It will be performed after the dbBaseline assessments of the entire study population have been completed. The study team will remain blinded to individual data. The details of the interim analyses/evaluation will be described in interim analysis charter.

8.1.8 Compliance

Treatment compliance will be calculated for each subject as the number of injections actually received divided by the number of injections should have received during the subject's participation in the study (rounded to 0.1%). Compliance will be summarized for All Treated Subjects.

8.2 Determination of Sample Size

The planned total number of subjects enrolled into the Lead-In Period is approximately 200.

A recently published study (DOSERA) showed that 56% (15/27 patients) of patients who were previously in low disease activity had treatment failure within 48 weeks after reducing the dose of etanercept; the median time to failure was 36 weeks (95% CI:15.6-NE).⁸⁹ The STRASS study, also published in 2015, showed in a similar RA

patient population, that progressive tapering of TNFi therapy (adalimumab or etanercept) was associated with flare in 76.6% (49/64) of patients throughout the study duration; importantly, 28.8% of patients flared after the first step of tapering (adalimumab 40 mg q3 weeks or etanercept 50 mg q10 days) and the median time to flare was 9 months.⁹⁰ In another tapering study (DRESS) a cumulative incidence of short-lived flares in a progressive tapering of TNFi of 55% at 9 months (and 73% at 18 months) was observed. Among these studies, the DRESS study had the higher sample size with 121 patients in the taper arm but only 43% successfully tapered the TNFi. None of these studies was designed or powered to evaluate predictors of flare neither found definite predictors upon further statistical analysis. A proof of concept study conducted in 44 RA patients in clinical remission receiving treatment with a bDMARD has shown that residual synovial inflammation determined by comprehensive ultrasound assessment predicted relapse within a short term after discontinuation of the treatment.⁹¹

These data provided the rationale for assuming a conservative flare rate of 30% and for our sample size calculation.

To estimate the odds ratio for the occurrence of flare with baseline MRI score based on historical MRI data, an effective sample size of 150 subjects in the dose tapering group will ensure a precision for the estimation with the width of 90% CI no more than 0.03 for an odds ratio 1.03, no more than 0.07 for an odds ratio 1.1, and no more than 0.14 for an odds ratio 1.2. Such sample size will also ensure a precision for the estimation of a correlation coefficient ρ with the width of 90% CI of ρ no more than 0.26 for a mild correlation coefficient 0.28, no more than 0.18 for a moderate correlation coefficient 0.55, and no more than 0.13 for a higher correlation with $\rho = 0.67$. Assuming a 30% flare rate, this sample size will provide the precision that the 2-sided 90% CI of the flare rate has a half width no more than 6%.

Sensitivity precision levels under various assumptions are presented in [Table 4](#).

Under a 5:1 randomization ratio (dose tapering versus withdrawal), a total of 180 subjects will be randomized. Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 200 subjects will need to be enrolled into the Lead-In Period.

Table 4. Sample Size Assumptions

True Odds Ratio	Flare Rate	Sample Size (Dose Tapering Arm)	OR from Logistics Regression (90% CI) : CI Width	Correlation (90% CI) : CI Width
1.03	30%	150	1.03 (1.02, 1.05) : 0.03	0.28 (0.14, 0.40) : 0.26
1.1	30%	150	1.1 (1.07, 1.14) : 0.07	0.55 (0.46, 0.64) : 0.18
1.2	30%	150	1.21 (1.15, 1.29) : 0.14	0.67 (0.61, 0.73) : 0.13

8.3 Randomization Methods

Subjects will be randomized to a standardized tapering scheme of adalimumab 40 mg sc every 3 weeks or placebo (drug withdrawal) in a 5:1 ratio at the beginning of double-blinded period of the study. Subjects experiencing a flare at any time point will be re-treated with open label adalimumab 40 mg eow.

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](#).

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.

At the time of blood draw for biomarkers, subjects in certain countries (where allowed by local guidelines) will have the option for serum to be stored for possible future research.

The storage of these biomarker samples for possible future research is optional and subjects' may decline at any time.

A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

The decision to allow pharmacogenetic analysis assessment will be determined by local regulations. Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent form, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The separate pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from

Investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

10.3 Electronic Patient Reported Outcomes (ePROs)

An electronic patient-recorded outcomes (ePRO) device will be provided to subjects during screening and will be completed at all subject visits in the office. An additional device will be given to subjects at their flare Week 0 visit (if applicable) and will be completed at home weekly. Site personnel will provide training on the proper use of the e-Diary. These data will be uploaded to a server, the data on the server will be considered source, and maintained and managed by CRF Health. Patient reported data are completed for each subject screened/enrolled in this study. An ePRO tool called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA, will be used to collect this data. The ePRO system is in compliance with Title 21 CFR Part 11.

Internet access to the ePRO data will be provided by CRF Health for the duration of the trial. This access will be available for the duration of the trial to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO 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 print-outs from that media.

The electronic device may be programmed to allow data entry for only certain periods of time. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

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

Please refer to the Investigator site contract for specific information related to publication practices.

AbbVie abides by the PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial results. AbbVie's registrations and results disclosure adhere to all relevant state and federal laws.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

Any pharmacogenetic research that may be done using DNA and mRNA samples from this study will be for research purposes only and the results will not be suitable for clinical decision-making or patient management. Hence, neither the Investigator, the subject, nor the subject's physician (if different than the Investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than in response to requests from health authorities. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator 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 (EMA) Guidance on Investigator's Signature for Study Reports.

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.

14.0 Investigator's Agreement

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

Protocol Title: A Phase 4 Trial Assessing the Impact of Residual Inflammation Detected via Imaging Techniques, Drug Levels and Patient Characteristics on the Outcome of Dose Tapering of Adalimumab in Clinical Remission Rheumatoid Arthritis (RA) Subjects (PREDICTRA)

Protocol Date: 25 February 2016

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

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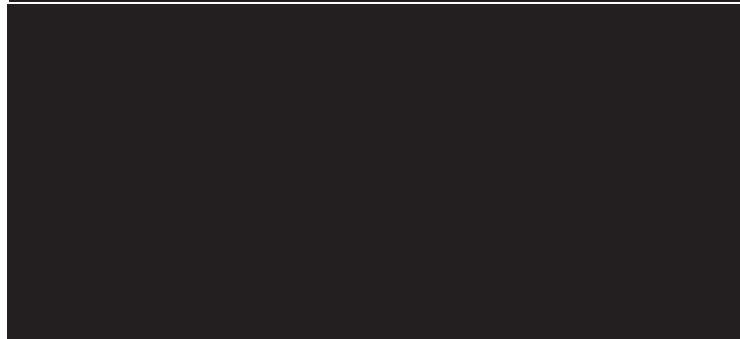
Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
		Global Medical Affairs
		Statistics
		Global Medical Affairs
		Clinical
		Pharmacokinetics
		Bioanalytics
		Regulatory Affairs
		Clinical

Appendix C. Injection Instructions – Pre-Filled Syringe – Sample

Subject Instructions

0.8 mL dose

(Administered as a single dose-pre-filled syringe)

Protocol M14-500

Table of Contents

Dosing Schedule

General Information and Supplies

Injection Procedures

Study Drug Dosing Schedule

Subject Number: _____

You will require subcutaneous (SC) injections throughout the study.

Call your doctor at any time if you feel that your disease is worsening.

You will receive the following number of injections during the study:

- At the Lead-In Week 0 Visit (the first visit to receive study medication for this study) you will receive 1 injection at the clinic (self-administer or receive help from site staff) and 1 injection to take 2 weeks after the Week 0 Visit.
- At Week 4 at the start of the Double-Blind Period, you will receive 2 syringes. At the Week 4 Visit, you will administer the injection at the clinic. You will take the other 1 syringe home to be administered at Week 7. During the remainder of the Double-Blind Period (Weeks 10, 16, 22, 28 and 34), you will receive 2 syringes at each visit to be taken (one to be administered at the visit and the other to be taken at home 3 weeks later) at Weeks 10, 13, 16, 19, 22, 25, 28, 31, 34 and 37, respectively.
- If at any time you have a flare and it is confirmed, you will enter the Open Label Rescue Arm and start a Flare Week 0 Visit. *You must return all double-blind medication at the next visit.*
 - At the Flare Week 0 Visit, you will receive 2 syringes. One injection of open-label adalimumab will be administered at the clinic. You will take the other 1 syringe home to be administered 2 weeks later at Flare Week 2.
 - At the Flare Week 4 and 10 Visits, you will receive 3 syringes at each visit (one to be administered at the visit and the other 2 to be taken separately at home every two weeks) to be taken at Flare Weeks 4, 6, 8, 10, 12, 14 respectively.
 - If your time of injection falls on a clinic day, you must inject study drug after all study procedures are performed (not prior).

Throughout the study, you will receive active study medication (or placebo). You or a trained designee will inject your study drug at the following timepoints:

- every other week in the Lead-In Period
- every 3 weeks in the Double-Blind Period
- every other week in the Open-Label Rescue Arm

If you meet the criteria for flare at any time during the Double-Blind Period, you will receive rescue therapy (active study drug) for 16 weeks. You will not administer study medication at your last visit.

Please return all used and unused syringes, the sharps container and empty boxes to the clinic on your next visit. Used syringes should be placed in the special Sharps container provided. All unused syringes should be returned in the original box.

If an injection is missed or something occurs where the full dose cannot be injected, contact your study center immediately for further instructions. Please record any missed doses on your subject dosing sheet.

Remember to complete your dosing sheet after each injection and to call the doctor's office if you are having problems administering your study medication.

General Information

- Pre-filled syringes with study medication will be labeled "Adalimumab" during the open-label period (Period 1) or during rescue therapy and "Adalimumab or Placebo" during the Double-Blind Period (Period 2).
- Store all pre-filled syringes in your refrigerator at 36° to 46°F (2° to 8°C) in the original container until it is used. NOT in the freezer. Should the syringes accidentally become frozen, call your study doctor's office.
- Protect the study medication from light.
- Do not use a pre-filled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.

- Do not drop or crush the study medication. The pre-filled syringe is glass.
- Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.
- **USE A NEW SYRINGE EVERY INJECTION DAY.** There may be medication left in the syringe. **DO NOT RE-USE.**
- Save all study medications. **Pre-filled syringes (used and unused) and empty boxes must be returned to the study center at each visit.** Used syringes will be disposed of in a sharps container provided to you.
- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call** _____, or proceed to your nearest emergency room.
- Keep study medication, injection supplies, and all other medicines out of the reach of children.

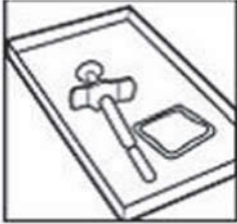
Injection Procedures (PFS)

1. Setting up for an injection

- Find a clean flat surface.
- Do not use if the seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one kit with the prefilled syringe(s) of adalimumab from the refrigerator. Do not use a prefilled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused syringe(s) to the refrigerator.

You will need the following items for each dose:

- study medication in pre-filled syringe(s)
- alcohol prep(s)
- cotton ball or gauze pad(s)

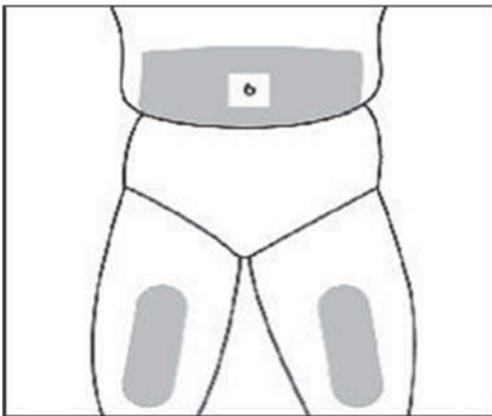


If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

- Make sure the liquid in the prefilled syringe is clear and colorless. Do not use a prefilled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a special sharps (puncture proof) container nearby for disposing of used needles and syringes.

For your protection, it is important that you follow these instructions.

2. Choosing and preparing an injection site

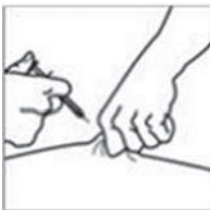


- Wash your hands well.

- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 2 inches around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- If you have psoriasis, you should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (swab), using a circular motion. Do not touch this area again until you are ready to inject.

3. How to prepare your adalimumab dose for injection with a Pre-filled Syringe

- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line for the 40 mg pre-filled syringe. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, do not use that syringe. Call your study doctor.
- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is okay.
- Do not shake the syringe.



4. Injecting Adalimumab

- With your other hand, gently squeeze an area of the cleaned area of skin and hold it firmly.
- You will inject into this raised area of skin. Hold the syringe like a pencil at about a 45° angle (see picture) to the skin.
- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger. If blood appears in the syringe it means that you have entered a blood vessel. Do not inject adalimumab. Pull the needle out of the skin and repeat the steps to choose and clean a new injection site. Do not use the same syringe. Dispose of it in your special sharps container. If no blood appears, slowly push the plunger all the way in until all of the adalimumab is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was pushed into the skin.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do not rub the injection site. You may have slight bleeding. This is normal.
- Dispose of the syringe right away into your special sharps container.

Appendix D. Subject Dosing Diary – Sample

To be completed for every study dose administered. Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor. Please record the date, time of study drug administration, kit number, dose administered, injection location, initials of person administering study medication, and any comments. Instructions on proper study medication administration will be provided by your study doctor and should be followed for every injection. Call the doctor's clinic if you are having problems administering your study medication.

Please bring your Sheet with you to each clinic visit.

If you have any questions or concerns at any time, please call the study coordinator or physician at the following number(s):

Date day/mm/yr	Day or Week #	Time of Study Drug Administration ^a	Kit Number	Dose (mL) Administered	Injection Site (abdomen or thigh)	Initials of Person Administering Study Medication	Comments
31/MAY/12	EXAMPLE	0 9:30 hrs	123456	0.8 mL	abdomen	PG	Clinic injection
Lead-In Period							
	Week 0	: hrs					
	Week 2	: hrs					
Randomized Double-Blind Period (once subject flares, mark N/A and move to Open-label Rescue Arm below)							
	Week 4	: hrs					
	Week 7	: hrs					
	Week 10	: hrs					
	Week 13	: hrs					
	Week 16	: hrs					
	Week 19	: hrs					
	Week 22	: hrs					
	Week 25	: hrs					
	Week 28	: hrs					
	Week 31	: hrs					
	Week 34	: hrs					
	Week 37	: hrs					
Open-Label Rescue Arm (adalimumab every other week for 16 weeks (otherwise, please mark "N/A"))							
	Flare Week 0	: hrs					
	Flare Week 2	: hrs					
	Flare Week 4	: hrs					

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Adalimumab
M14-500 Protocol Amendment 1
EudraCT 2014-001114-26

Date day/mm/yr	Day or Week#	Time of Study Drug Administration ^a	Kit Number	Dose (mL) Administered	Injection Site (abdomen or thigh)	Initials of Person Administering Study Medication	Comments
	Open-Label Rescue Arm	adalimumab every other week for 16 weeks (otherwise, please mark "N/A")					
	Flare Week 6	: hrs					
	Flare Week 8	: hrs					
	Flare Week 10	: hrs					
	Flare Week 12	: hrs					
	Flare Week 14	: hrs					

a. Please note the time in military time (e.g., 22:00 hours etc.).

Appendix E. Joint Evaluation Worksheet – Sample

JOINT EVALUATION												
JOINT (Tick Correct Answer)	Subject Right						Subject Left					
	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
	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
27. Metatarsophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA

JOINT EVALUATION												
JOINT (Tick Correct Answer)	Subject Right						Subject Left					
	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
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 F. DAS28 Joint Assessment

Out of the 68 tender and 66 swollen evaluated, the following 28 joints are include in DAS28 calculation. DAS28 will be calculated by the eCRF.

Example of the 28 joints assessed for DAS28:

		Left		Right	
		Swollen	Tender	Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		Swollen		Tender	

Appendix G. Health Assessment Questionnaire (HAQ-DI) – Sample

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 <u>ANY</u> DIFFICULTY	WITH <u>SOME</u> DIFFICULTY	WITH <u>MUCH</u> DIFFICULTY	<u>UNABLE</u> TO DO
<u>DRESSING AND GROOMING</u>				
Are you able to:				
Dress yourself, including tying shoelaces and doing buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>ARISING</u>				
Are you able to:				
Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>EATING</u>				
Are you able to:				
Cut your own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<u>WALKING</u>				
Are you able to:				
Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

- | | |
|-------------------------------------|---|
| <input type="checkbox"/> Cane | <input type="checkbox"/> Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.) |
| <input type="checkbox"/> Walker | <input type="checkbox"/> Built up or special utensils |
| <input type="checkbox"/> Crutches | <input type="checkbox"/> Special or built up chair |
| <input type="checkbox"/> Wheelchair | <input type="checkbox"/> Other (Specify: _____) |

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

- | | |
|--|----------------------------------|
| <input type="checkbox"/> Dressing and Grooming | <input type="checkbox"/> Eating |
| <input type="checkbox"/> Arising | <input type="checkbox"/> Walking |

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

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

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

- | | |
|--|--|
| <input type="checkbox"/> Raised toilet seat | <input type="checkbox"/> Bathtub bar |
| <input type="checkbox"/> Bathtub seat | <input type="checkbox"/> Long-handled appliances for reach |
| <input type="checkbox"/> Jar opener (for jars previously opened) | <input type="checkbox"/> Long-handled appliances in bathroom |
| | <input type="checkbox"/> Other (Specify: _____) |

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

- | | |
|----------------------------------|--|
| <input type="checkbox"/> Hygiene | <input type="checkbox"/> Gripping and opening things |
| <input type="checkbox"/> Reach | <input type="checkbox"/> Errands and chores |

Appendix H. FACIT-Fatigue Scale (Version 4) English Version – Sample

Below is a list of statements that other people with your illness have said are important.

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	Not at All	A little bit	Some- what	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless ("washed out")	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

**Appendix I. Treatment Satisfaction Questionnaire for Medication (TSQM) –
Sample**

TSQM (Version 1.4)

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
 - 1 Extremely Dissatisfied
 - 2 Very Dissatisfied
 - 3 Dissatisfied
 - 4 Somewhat Satisfied
 - 5 Satisfied
 - 6 Very Satisfied
 - 7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
 - 1 Extremely Dissatisfied
 - 2 Very Dissatisfied
 - 3 Dissatisfied
 - 4 Somewhat Satisfied
 - 5 Satisfied
 - 6 Very Satisfied

7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

1 Extremely Dissatisfied

2 Very Dissatisfied

3 Dissatisfied

4 Somewhat Satisfied

5 Satisfied

6 Very Satisfied

7 Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

1 Yes

0 No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

1 Extremely Bothersome

2 Very Bothersome

3 Somewhat Bothersome

4 A Little Bothersome

5 Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

1 A Great Deal

2 Quite a Bit

3 Somewhat

4 Minimally

5 Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?
- 1 A Great Deal
 - 2 Quite a Bit
 - 3 Somewhat
 - 4 Minimally
 - 5 Not at All
8. To what degree have medication side effects affected your overall satisfaction with the medication?
- 1 A Great Deal
 - 2 Quite a Bit
 - 3 Somewhat
 - 4 Minimally
 - 5 Not at All
9. How easy or difficult is it to use the medication in its current form?
- 1 Extremely Difficult
 - 2 Very Difficult
 - 3 Difficult
 - 4 Somewhat Easy
 - 5 Easy
 - 6 Very Easy
 - 7 Extremely Easy
10. How easy or difficult is it to plan when you will use the medication each time?
- 1 Extremely Difficult
 - 2 Very Difficult
 - 3 Difficult
 - 4 Somewhat Easy
 - 5 Easy

- 6 Very Easy
- 7 Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

- 1 Extremely Inconvenient
- 2 Very Inconvenient
- 3 Inconvenient
- 4 Somewhat Convenient
- 5 Convenient
- 6 Very Convenient
- 7 Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

- 1 Not at All Confident
- 2 A Little Confident
- 3 Somewhat Confident
- 4 Very Confident
- 5 Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

- 1 Not at All Certain
- 2 A Little Certain
- 3 Somewhat Certain
- 4 Very Certain
- 5 Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

- 1 Extremely Dissatisfied
- 2 Very Dissatisfied
- 3 Dissatisfied
- 4 Somewhat Satisfied
- 5 Satisfied
- 6 Very Satisfied
- 7 Extremely Satisfied

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**Appendix J. Work Productivity and Activity Impairment (WPAI) – Sample
Rheumatoid Arthritis V2.0 (WPAI:RA)**

The following questions ask about the effect of your rheumatoid arthritis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

Are you currently employed (working for pay)? _____ NO ___ YES
If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

During the past seven days, how many hours did you miss from work because of problems associated with your rheumatoid arthritis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your rheumatoid arthritis. Do not include time you missed to participate in this study.*

_____ HOURS

During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____ HOURS

During the past seven days, how many hours did you actually work?

_____ HOURS *(If "0," skip to question 6.)*

During the past seven days, how much did your rheumatoid arthritis affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If rheumatoid arthritis affected your work only a little, choose a low number. Choose a high number if rheumatoid arthritis affected your work a great deal.

Consider only how much rheumatoid arthritis affected productivity while you were working.

Rheumatoid arthritis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Rheumatoid arthritis completely prevented me from working
---	---	---	---	---	---	---	---	---	---	---	----	---

CIRCLE A NUMBER

During the past seven days, how much did your Rheumatoid arthritis affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If rheumatoid arthritis affected your activities only a little, choose a low number. Choose a high number if rheumatoid arthritis affected your activities a great deal.

Consider only how much rheumatoid arthritis affected your ability to do your regular daily activities, other than work at a job.

Rheumatoid arthritis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Rheumatoid arthritis completely prevented me from doing my daily activities
---	---	---	---	---	---	---	---	---	---	---	----	---

CIRCLE A NUMBER

WPAI:RA V2.0 (US English)

f:\institut\cultadap\project\3339\study3339\final_versions\wpai-rausaoriq.doc-10/01/2007

Appendix K. Short Form-36 (SF-36) Health Survey Questionnaire – Sample

Your Health and Well-Being

SF-36v2[®] Health Survey[©] 1992, 1996, 2000, 2010
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United States (English))

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one box that best describes your answer.

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

Compared to one year ago, how would you rate your health in general now?

- Much better now than one year ago
- Somewhat better now than one year ago
- About the same as one year ago
- Somewhat worse now than one year ago
- Much worse now than one year ago

The following question is about activities you might do during a typical day.

Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in lifting or carrying groceries? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in climbing several flights of stairs? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in climbing one flight of stairs? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in bending, kneeling, or stooping? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in walking more than a mile? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in walking several hundred yards? If so, how much?

Yes, limited a lot
Yes, limited a little
No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in walking one hundred yards? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in bathing or dressing yourself? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Cut down on the amount of time you spent on work or other activities as a result of your physical health

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Accomplished less than you would like as a result of your physical health

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Were limited in the kind of work or other activities as a result of your physical health

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all
Slightly
Moderately
Quite a bit
Extremely

How much bodily pain have you had during the past 4 weeks?

None
Very mild
Mild
Moderate
Severe
Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all
A little bit
Moderately
Quite a bit
Extremely

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel full of life?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been very nervous?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt calm and peaceful?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you have a lot of energy?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt downhearted and depressed?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel worn out?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been happy?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel tired?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

How TRUE or FALSE is the following statement for you?

I seem to get sick a little easier than other people.

- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

How TRUE or FALSE is the following statement for you?

I am as healthy as anybody I know.

- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

How TRUE or FALSE is the following statement for you?

I expect my health to get worse.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

My health is excellent.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

Appendix L. RAPID-3 Questionnaire/Assessment (in office and at home) –

RAPID-3

ROUTINE ASSESSMENT OF PATIENT INDEX DATA

The RAPID3 includes a subset of core variables found in the Multi-dimensional HAQ (MD-HAQ). Page 1 of the MD-HAQ, shown here, includes an assessment of physical function (section 1), a patient global assessment (PGA) for pain (section 2), and a PGA for global health (section 3). RAPID3 scores are quickly tallied by adding subsets of the MD-HAQ as follows:

1. PLEASE CHECK THE ONE BEST ANSWER FOR YOUR ABILITIES AT THIS TIME:				
OVER THE LAST WEEK, WERE YOU ABLE TO:	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
a. Dress yourself, including tying shoelaces and doing buttons?	___ 0	___ 1	___ 2	___ 3
b. Get in and out of bed?	___ 0	___ 1	___ 2	___ 3
c. Lift a full cup or glass to your mouth?	___ 0	___ 1	___ 2	___ 3
d. Walk outdoors on flat ground?	___ 0	___ 1	___ 2	___ 3
e. Wash and dry your entire body?	___ 0	___ 1	___ 2	___ 3
f. Bend down to pick up clothing from the floor?	___ 0	___ 1	___ 2	___ 3
g. Turn regular faucets on and off?	___ 0	___ 1	___ 2	___ 3
h. Get in and out of a car, bus, train, or airplane?	___ 0	___ 1	___ 2	___ 3
i. Walk two miles or three kilometers, if you wish?	___ 0	___ 1	___ 2	___ 3
j. Participate in recreational activities and sports as you would like, if you wish?	___ 0	___ 1	___ 2	___ 3
k. Get a good night's sleep?	___ 0	___ 1.1	___ 2.2	___ 3.3
l. Deal with feelings of anxiety or being nervous?	___ 0	___ 1.1	___ 2.2	___ 3.3
m. Deal with feelings of depression or feeling blue?	___ 0	___ 1.1	___ 2.2	___ 3.3

L + J FN (0-10):

1-0.3 16-5.3
2-0.7 17-5.7
3-1.0 18-6.0
4-1.3 19-6.3
5-1.7 20-6.7
6-2.0 21-7.0
7-2.3 22-7.3
8-2.7 23-7.7
9-3.0 24-8.0
10-3.3 25-8.3
11-3.7 26-8.7
12-4.0 27-9.0
13-4.3 28-9.3
14-4.7 29-9.7
15-5.0 30-10

2. PN (0-10):

3. PTGE (0-10):

RAPID3 (0-30)

2. HOW MUCH PAIN HAVE YOU HAD BECAUSE OF YOUR CONDITION OVER THE PAST WEEK? PLEASE INDICATE BELOW HOW SEVERE YOUR PAIN HAS BEEN:																				
NO PAIN					PAIN AS BAD AS IT COULD BE															
0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10

3. CONSIDERING ALL THE WAYS IN WHICH ILLNESS AND HEALTH CONDITIONS MAY AFFECT YOU AT THIS TIME, PLEASE INDICATE BELOW HOW YOU ARE DOING:																				
VERY WELL					VERY POORLY															
0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10

CONVERSION TABLE
 Near Remission (NR): 1-0.3; 2-0.7; 3-1.0
 Low Severity (LS): 4-1.3; 5-1.7; 6-2.0
 Moderate Severity (MS): 7-2.3; 8-2.7; 9-3.0; 10-3.3; 11-3.7; 12-4.0
 High Severity (HS): 13-4.3; 14-4.7; 15-5.0; 16-5.3; 17-5.7; 18-6.0; 19-6.3; 20-6.7; 21-7.0; 22-7.3; 23-7.7; 24-8.0; 25-8.3; 26-8.7; 27-9.0; 28-9.3; 29-9.7; 30-10.0

HOW TO CALCULATE RAPID 3 SCORES

1. Ask the patient to complete questions 1, 2, and 3 while in the waiting room prior to his/her visit.
2. For question 1, add up the scores in questions A-J only (questions K-M have been found to be informative, but are not scored formally). Use the formula in the box on the right to calculate the formal score (0-10). For example, a patient whose answers total 19 would score a 6.3. Enter this score as an evaluation of the patient's functional status (FN).
3. For question 2, enter the raw score (0-10) in the box on the right as an evaluation of the patient's pain tolerance (PN).
4. For question 3, enter the raw score (0-10) in the box on the right as an evaluation of the patient's global estimate (PTGE).
5. Add the total score (0-30) from questions 1, 2, and 3 and enter them as the patient's RAPID 3 cumulative score. Use the final conversion table to simplify the patient's weighed RAPID 3 score. For example, a patient who scores 11 on the cumulative RAPID 3 scale would score a weighed 3.7. A patient who scores between 0-1.0 is defined as near remission (NR); 1.3-2.0 as low severity (LS); 2.3-4.0 as moderate severity (MS); and 4.3-10.0 as high severity (HS).

Appendix M. MRI Assessments and Scoring – Sample

MRI will be performed and assessed following the OMERACT MRI in RA group recommendations of a core set of basic MRI sequences, MRI definitions of important RA joint pathologies, and an RA MRI scoring system (OMERACT 2002 RAMRIS).

MRI images will be obtained from the most affected by RA wrist and hand (2nd – 5th MTP) using high-field and gadolinium contrast acquisition; if both are considered equally affected, the dominant wrist and hand will be scanned.

Clinical assessor will be blind for MRI scoring. Images will be sent for 1 – 2 central readers blinded for clinical parameters for assessment of all MRI images.

The pre-requirements for the MRI machines specifications, for the core set of basic MRI sequences acquiring as well as the detailed scoring system for synovitis, bone marrow oedema and tenosynovitis will be further detailed in an MRI manual.

Appendix N. Ultrasound Assessments and Scoring – Sample

For the sites that will be part of the optional Ultrasound assessment, Grey Scale-Ultrasound (GSUS) as well as Power-Doppler Ultrasound (PDUS) will be performed to all subjects included in the study at the defined time points of the protocol.

In light of the current evidence, 46-joint validated assessment and 18 tendon/tendon compartment assessment will be performed with the inclusion of the following bilateral:

- Joints: glenohumeral (i.e., posterior and axillary recesses and biceps sheath), elbow (i.e., anterior, posterior and lateral recesses), wrist (i.e., radio-carpal, midcarpal, and distal radioulnar joints; dorsal recesses), first through fifth metacarpophalangeal (PIP) of the hands (i.e., dorsal and palmar recesses), hip (i.e., anterior recess), knee (i.e., anterior and parapatellar recesses) ankle joints (i.e., anterior, lateral, and medial recesses of tibiotalar joint; and medial and lateral recesses of subtalar joint), and second and fifth metatarsophalangeal joints (i.e., dorsal recess). Joints will be investigated for the presence of intra-articular B-mode synovial hypertrophy (SH) and synovial Power Doppler (PD) signal. Ankle SH or synovial PD signal positive will be considered if they were detected in either the tibiotalar or the subtalar joints
- Tendons: 2nd, 4th and 6th extensor compartments at the wrist, 2nd – 5th finger flexor tendons, tibialis posterior and peroneal tendons. Tendons will be assessed for GS and Doppler tenosynovitis.

Intra-articular synovial hypertrophy (SH) will be defined according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) as the presence of abnormal hypoechoic (relative to subdermal fat) intraarticular tissue that is nondisplaceable and poorly compressible.

At each intra-articular synovial recess, B-mode SH will be scored semiquantitatively on a scale of 0 – 3 (0, absent; 1, mild; 2, moderate; 3, marked).

Synovial PD signal will be also scored on a semiquantitative scale of 0 – 3 (0, no synovial PD signal; 1, mild [≤ 3 PD signals within the SH]; 2, moderate [> 3 PD signals in less

than half of the SH area]; 3, marked [PD signals in more than half of the SH area]). Each joint was scored for B-mode SH and synovial PD signal on a scale from 0 to 3. These scores will correspond to the maximum score for SH and PD signal, respectively, obtained from any one of the synovial sites evaluated at each joint. GS and Doppler tenosynovitis will be defined and scored according to OMERACT.^{83,84-86}

Technical Requirements:

Different models of ultrasound machines are allowed as long as GS and PD are available. It's recommended to use high-end machines as per the training manual which will be provided.

US Assessment Conditions:

The US assessments are to be performed during the Screening or Lead-In Period prior to dbBaseline Visit by an expert in musculoskeletal ultrasound with verifiable training and/or certification and at least 3 years of experience. Ideally, the Ultrasonographer should have prior experience in multicenter study(ies) using ultrasound evaluation in RA patients; otherwise training will be provided. All ultrasound assessors will be provided with more details in a US manual. Ideally the same assessor at each site should perform all US evaluations. The US assessor will be blinded to clinical parameters and the clinical assessor will be blinded to US scoring.

B-mode and PD machine settings will be optimized before the study and standardized for the whole study. The US assessment should be performed in a darkened room with temperature kept stable. Patients should have been at least 2 hours resting, and should not have drunk coffee, alcohol, smoked cigarettes or practiced sport within the prior 8 hours or taking NSAIDs within the prior 12 hours.

Further details will be provided in the US manual.

Appendix O. ACR 1987 and the ACR/EULAR 2010 Criteria for Classifying RA

The 1987 Criteria for the Classification of RA⁸⁷

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting for at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissues swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joints areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in < 5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on posteranterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

For classification purposes, a patient is said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite or probable RA is not to be made.

The 2010 ACR-EULAR classification criteria for rheumatoid arthritis.⁸⁸

Target population (Who should be tested?): Patients who:

1. Have at least 1 joint with definite clinical synovitis (swelling)*
2. With the synovitis not better explained by another disease

Classification criteria for RA (score-based algorithm: add score of categories A – D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)	Score
A. Joint involvement	
1 large joint	0
2 – 10 large joints	1
1 – 3 small joints (with or without involvement of large joints)	2
4 – 10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF <i>and</i> negative ACPA	0
Low-positive RF <i>or</i> low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP <i>and</i> normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

â€ Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

â€ Although patients with a score of < 6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

Â§ Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

¶ "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

** In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

- â€ â€ Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.
- â€;â€; Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
- Â§Â§ Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix P. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page

"Sponsor:" previously read:

Sponsor:	For Non-EU Countries: AbbVie 1 North Waukegan Road ██████████ North Chicago, IL 60064	For EU Countries: AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany
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Has been changed to read:

Sponsor:	For Non-EU Countries: AbbVie 1 North Waukegan Road ██████████ North Chicago, IL 60064	For EU Countries: AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany
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Section 1.1 Synopsis

Previously read:

AbbVie Inc.	Protocol Number: M14-500
Name of Study Drug: Adalimumab	Phase of Development: 4
Name of Active Ingredient: Adalimumab	Date of Protocol Synopsis: 15 May 2014
Protocol Title: A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected via Imaging TEchniques Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA)	

Objectives:

The **primary objective** is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects randomized to an adalimumab dose tapering regimen controlled by adalimumab withdrawal.

The **Secondary Objectives** are:

- To assess the occurrence and severity of flares and the time to flare in both taper and withdrawal arms.
- To investigate the association between Double-Bind Baseline (dbBaseline) subject demographic and disease characteristics and the occurrence of flares.
- To investigate the association between dbBaseline adalimumab trough concentrations and the occurrence of flares.
- To evaluate the effectiveness of rescue therapy with open-label adalimumab 40 mg every other week (eow) over 16 weeks in subjects experiencing a flare.
- To assess the change in rheumatoid arthritis MRI scoring system (RAMRIS) scores from Baseline to Final visit in the taper, withdrawal and Open-Label Rescue Arms.
- To describe the course of disease using clinical and patient reported outcomes (PROs) measures in the taper, withdrawal and Open-Label Rescue Arms.
- To assess the rate of anti-adalimumab antibodies (AAA) positive subjects in the taper and withdrawal arms.

The study also has the following exploratory objectives:

- In the subgroup of subjects with a dbBaseline Ultrasound (US) assessment:
 - To investigate the association between dbBaseline ultrasound scores and the occurrence of flares.
 - To investigate the association between the dbBaseline ultrasound scores and Baseline MRI RAMRIS scores.
 - To describe the change in the ultrasound scores from dbBaseline to the time of the occurrence of a flare in the taper and withdrawal arms.
- To investigate the association between biomarker values at dbBaseline (or their change over time) and the occurrence of flares.

Investigators: Investigator information is on file at AbbVie.

Study Sites: Approximately 53 sites

Study Population:

Subjects age ≥ 18 years diagnosed with RA, on a stable dose of adalimumab 40 mg subcutaneously (sc) eow (for ≥ 12 months prior to Screening Visit) in combination with methotrexate (MTX) (at stable dose for ≥ 12 weeks prior to the Screening Visit) and in documented clinical remission, defined as DAS28 erythrocyte sedimentation rate (ESR) < 2.6 or DAS28 c-reactive protein (CRP) < 2.6 , for ≥ 6 months prior to the Screening Visit and DAS28 (ESR) < 2.6 at the Screening Visit.

Number of Subjects to be Enrolled: Approximately 334

Methodology:

This is a Phase 4, multicenter, randomized, double-blind, parallel-group study in subjects with RA who are in stable clinical remission defined as DAS28 (ESR) or DAS28 (CRP) < 2.6 for at least 6 months prior to the Screening Visit. Though the cut-off for clinical remission of DAS28 (CRP) may not be equivalent to the DAS (ESR), in clinical practice both are frequently used to define remission as < 2.6. Both will be allowed for the purposes of identifying subjects for Screening; however, throughout the study clinical remission will be defined by the more stringent DAS28 (ESR) < 2.6 criteria. At Screening, only subjects with confirmed DAS28 (ESR) < 2.6 will be considered for inclusion in the study.

The study activities will start with a Screening Period of up to 21 days to confirm inclusion/exclusion criteria including a DAS28 (ESR) assessment of < 2.6.

Subjects who have signed the Informed Consent and who fulfill all Screening criteria will enter the study. Study starts with a 4-week Lead-In Open-Label (OL) Period during which stable DAS28 (ESR) clinical remission in 2 assessments 4 weeks apart will be confirmed. Subjects will receive adalimumab 40 mg sc eow starting at Week 0 Visit of the Lead-In Period; this will be approximately 2 weeks after their last commercial Humira[®].

At Week 4, the end of the Lead-In Period, subjects will have a dbBaseline visit. Subjects must have a confirmed DAS28 (ESR) remission at two time points in order to be randomized:

1. DAS28 (ESR) < 2.6 at the Lead-In Period Week 0
2. DAS28 (ESR) < 2.6 at the dbBaseline visit Week 4

Subjects who meet the remission criteria will be randomized (5:1) to one of two double-blind arms and followed for additional 36 weeks in the Double-Blind Period:

1. A reduced frequency of adalimumab 40 mg sc every 3 weeks (q3wks): taper arm, or
2. Adalimumab placebo sc q3wks: withdrawal arm.

All subjects will maintain the required MTX (any dose; oral or sc) at a stable dose for at least 12 weeks prior to Screening and throughout the Lead-In and Double-Blind Periods of study.

Any other allowed RA concomitant medications should also be kept stable throughout the Lead-In and Double-Blind Periods of the study; these medications and MTX will be received by local prescriptions.

During the Double-Blind Period, subjects will be evaluated every 6 weeks for efficacy, including detection of flares, PROs, safety and laboratory assessments at scheduled visits on: Weeks 4, 10, 16, 22, 28, 34 and 40 (Final visit).

Other unscheduled visits will occur in the suspected event of a flare. During the interval between scheduled visits, subjects will be asked to contact their physicians in case of feeling their disease is worsening: an unscheduled visit will be performed within 2 weeks of contact with the site to assess if subjects are experiencing a flare.

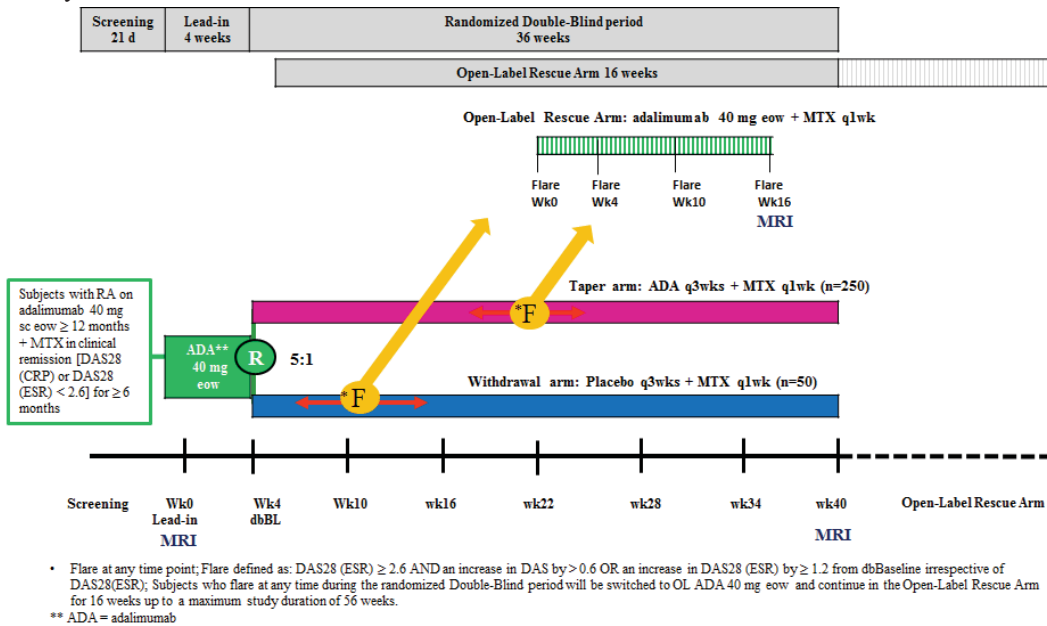
Methodology (Continued):

Subjects with a confirmed flare (defined as an increase from dbBaseline in DAS28 [ESR] of > 0.6 AND a DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR]) at any time point (at a scheduled or unscheduled visit) will undergo Flare Week 0 visit procedures and will be immediately switched to an Open-label rescue arm initiating adalimumab 40 mg eow rescue therapy.

In the Open-Label Rescue Arm, subjects will be further evaluated at Flare Weeks 4, 10 and 16 for efficacy, PROs, safety and laboratory assessments.

During this period, further treatment escalation/change will be allowed based on the Investigator's medical judgment. Any treatments escalation/change will be documented. At Flare Week 0, all subjects will be requested to initiate weekly at home self-assessment of their RA disease activity by using Routine Assessment of Patient Index Data (RAPID)-3 questionnaire until Week 16.

See study schematic below:



A high-field contrast MRI of the most affected or of the dominant hand (2nd to 5th MCP) and wrist (if both sides are considered equally affected), will be performed on all subjects during the Lead-In Period (prior to the dbBaseline visit) and at Final/Early Termination Visit.

The acquired MRI images will be centrally read and Investigators will be blinded to the results. Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.

Methodology (Continued):

In sites that meet pre-specified ultrasound requirements and who wish to participate in the ultrasound portion of the study, subjects will undergo US assessment using Gray Scale Ultrasonography (GSUS) and Power Doppler Ultrasonography (PDUS) consisting in a systematic longitudinal and transverse multiplanar examination of 46 joints and 18 tendon/tendon compartment during Lead-In or at dbBaseline Visit prior to randomization and at the Flare Week 0 Visit (if applicable). US will be performed and assessed by local Ultrasonographer independent of the clinical assessor who will be blinded to the US scores.

Pharmacokinetics (PK) and immunogenicity will be assessed based on serum adalimumab trough concentrations and serum anti-adalimumab antibodies (AAA), respectively. Blood samples for adalimumab concentrations and measurements of AAA will be taken prior to dosing at dbBaseline (Week 4), at Weeks 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable).

A panel of inflammatory biomarkers: matrix metalloproteinase 3 (MMP3), Collagen neo-epitope (C1M), Type III collagen neo-epitope (C3M), Matrix metalloproteinase-mediated c-reactive protein (CRPM), Matrix metalloproteinase-degraded citrullinated vimentin (VICM), Serum amyloid-associated protein (SAA), Interleucin-6 (IL-6), Chemokine (C-X-C motif) ligand 10 CXCL10 and CXCL13 will be assessed at dbBaseline (Week 4), Weeks 10, 16, 28, 40 or at Early Termination, Flare Weeks 0, 4 and 16 (if applicable) on blood samples taken prior to dosing. At the time of analysis, other potential biomarkers identified as adding value to predict flare in this patient population may be included.

Additional optional samples for future biomarker research will be collected.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female subjects ≥ 18 years of age.
2. Subject has a diagnosis of RA as defined by the 1987 revised ACR classification criteria and/or the ACR/EULAR 2010 classification criteria (any duration since diagnosis).
3. Subject must meet the following criteria:
 - Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Screening Visit;
 - Must be treated with concomitant MTX at a stable dose (oral or sc at any dose) for at least 12 weeks prior to Screening Visit.
4. Subject must be in sustained clinical remission based on the following:
 - At least one documented DAS28 (ESR) or DAS28 (CRP) < 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
 - DAS28 (ESR) assessed at Screening < 2.6 , with all components including ESR assessed at Screening.
5. If subjects are receiving concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in addition to MTX, the dose must be stable for at least 12 weeks prior to the Screening Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
6. If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to the Screening Visit.
7. If subjects are receiving non-steroidal anti-inflammatory drugs (NSAIDs) the dose must be stable for at least 4 weeks prior to the Screening Visit.
8. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

<p>Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):</p> <p>Main Exclusion:</p> <ol style="list-style-type: none"> 1. Any DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit ≥ 2.6. 2. Subject is on an additional concomitant biological disease-modifying anti-rheumatic drug (bDMARD) (including but not limited to abatacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab or tocilizumab). 3. Subject has been treated with intra-articular or parenteral corticosteroids within the last 4 weeks before Screening. 4. Subject has undergone joint surgery within 12 weeks of Screening (at joints to be assessed by MRI and/or ultrasound). 5. Subject has a medical condition precluding an MRI (e.g., magnetic activated implanted devices – cardiac pace-maker, insulin pump, neurostimulators, etc. and metallic devices or fragments or clips in the eye, brain or spinal canal and in the hand/wrist undergoing MRI). 6. Subject has a medical condition precluding a contrast MRI with gadolinium (e.g., nephrogenic systemic fibrosis, previous anaphylactic/anaphylactoid reaction to gadolinium containing contrast agent, pregnancy or breastfeeding, severe renal insufficiency with an estimated Glomerular Filtration Rate [eGFR] below 30 mL/min/1.73 m² at Screening, hepato-renal syndrome, severe chronic liver function impairment). 7. Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Screening Visit. 	
Investigational Product:	Adalimumab
Dose:	Lead-In Period: Adalimumab 40 mg OL eow for 4 weeks Double-Blind Period: Adalimumab 40 mg q3wks for 36 weeks Open-Label Rescue Arm: Adalimumab 40 mg OL eow for a minimum of 16 weeks
Mode of Administration:	Subcutaneously (SC) pre-filled syringe
Reference Therapy:	Placebo for the Double-Blind Period
Dose:	0.8 ml q3wks
Mode of Administration:	Subcutaneously (SC) pre-filled syringe
Duration of Treatment:	The duration of treatment will include a 4-week Lead-In Period (adalimumab 40 mg sc eow) followed by a 36-week, randomized, Double-Blind Period with 2 arms: taper arm (adalimumab 40 mg sc q3wks) controlled by matching placebo. Open-Label Rescue Arm (adalimumab 40 mg sc eow) will be provided for 16 weeks (if applicable). Therefore, the total duration of the study is 40 or 56 weeks (if applicable).

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variables

- The primary explanatory variables are the Baseline hand and wrist synovitis and bone marrow edema (BME) RAMRIS scores as well as a composite of both and the dependent variable is the occurrence of flare up to Week 40 in the tapering arm.

Secondary Variables

- Time to flare
- Flare severity
- Proportion of subjects experiencing a flare
- Subject demographics and clinical disease characteristics at dbBaseline, including
 - Smoking status, co-morbidities, anti-citrullinated peptide antibody (ACPA) status, Rheumatoid Factor (RF) status, disease duration, previous treatment with conventional synthetic Disease Modifying Anti-rheumatic Drugs (csDMARDs) or biologic Disease Modifying Anti-rheumatic Drugs (bDMARDs) or both, duration of adalimumab therapy, remission duration, disease activity, c-reactive protein (CRP) and Health Assessment Questionnaire (HAQ) score
- Proportion of subjects who regain clinical remission (defined as DAS28 [ESR] < 2.6 and defined as DAS28 (ESR) decrease > 1.2 if DAS28 [ESR] was less than 2.6 at flare) in the Open-Label Rescue Arm over time
- Time to regain clinical remission in the Open-Label Rescue Arm
- Proportion of subjects with low disease activity (defined as DAS28 [ESR] < 3.2) in the Open-Label Rescue Arm over time
- Change from Baseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)
- Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI: DAS28 [ESR] < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8) throughout the study
- Change from dbBaseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores
- Change from Baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) over time
- Proportion of subjects with HAQ-DI normal (HAQ-DI ≤ 0.5) at dbBaseline and at Week 40
- Change from dbBaseline in RAPID 3 scores assessed during Visits
- Change from Flare Week 0 in RAPID 3 at home assessments
- Change from dbBaseline in Swollen Joint Count (both 28 and 66 joints)
- Change from dbBaseline in Tender joint Count (both 28 and 68 joints)
- Change from dbBaseline in Patient's Global Assessment of Disease activity
- Change from dbBaseline in Patient's Global Assessment of RA pain
- Change from dbBaseline in Physician's Global Assessment of Disease activity
- Change from dbBaseline in morning stiffness assessment
- Change from dbBaseline in Sleep disturbance assessment
- Change from dbBaseline in Treatment Satisfaction Questionnaire for Medication (TSQM)
- Change from dbBaseline in Work Productivity and Activity Impairment (WPAI)

Criteria for Evaluation (Continued):

Efficacy(Continued):

Secondary Variables (Continued):

- Change from dbBaseline in Short Form-36 (SF-36)
- Change from dbBaseline in Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-fatigue)
- Change from dbBaseline in CRP
- Change from dbBaseline in ESR

Exploratory Variables

- dbBaseline and change from dbBaseline to the time of flare in PDUS and GSUS individual and composite scores of synovitis, synovial hypertrophy and tenosynovitis
- dbBaseline and change from dbBaseline on biomarker values (MMP3, SAA, C1M, C3M, CRPM, VICM, IL-6, CXCL10, CXCL13)

Pharmacokinetics:

- Adalimumab concentrations measurement dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable)
- AAA measurement at dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4, 10 and 16 (if applicable)

Safety:

Screening assessments will include medical history, vital signs, physical examination, and clinical and laboratory tests. The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, physical examination (if required) and laboratory tests.

Interim Analysis for Double-Blind Baseline Characteristics:

There are few data describing patient disease characteristics, including markers of residual inflammation (such as sensitive imaging assessments and potential biomarkers) and drug levels in patients who are in sustained RA clinical remission on a stable treatment with a TNFi and MTX. An interim analysis will be conducted to describe the dbBaseline characteristics of this RA population. It will be performed after the dbBaseline assessments and randomization of the entire study population have been completed.

Statistical Methods:

Efficacy:

Analysis for Primary Objective:

The association between the occurrence of flares and Baseline MRI RAMRIS scores will be examined using logistic regression, which is deemed as the main analysis to address the primary objective. Additional analyses will be performed to assess this association using various statistical methods. Specifically, descriptive statistics of Baseline MRI RAMRIS scores will be provided for the two groups of subjects who flare and who do not flare, and the between-group difference in the mean scores will be computed together with a 90% confidence interval (CI). Linear regression will be used to model the relationship between the DAS28 (ESR) at flaring (or at end of study for subjects who do not flare) and the Baseline MRI RAMRIS scores. Receiver operating characteristic (ROC) curve approach will also be utilized to investigate the potential flare prediction criteria based on MRI RAMRIS scores. All model based analyses may adjust for dbBaseline clinical patient characteristics including disease duration, previous treatment, etc. when appropriate.

Similar analysis will be conducted for RAMRIS synovitis scores, BME scores and the composite of both.

Analysis for Secondary Objectives:

Within the analyses to address the secondary objectives the association between dbBaseline disease characteristics and the occurrence of flares will be examined using similar analyses as for the primary objective. In addition, characterization of flares, response to rescue therapy in subjects experiencing a flare and the clinical and patient reported efficacy outcomes for all trial subjects will be analyzed accordingly.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by treatment arm at each time point using descriptive statistics. The association between dbBaseline adalimumab trough concentrations and the occurrence of flares will be assessed. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

AAA will be evaluated for each subject and each study arm, and rates of AAA positive subjects will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment emergent adverse events may be evaluated.

Safety:

Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA) 17.0 dictionary, by system organ class and by causality to the study medication as assessed by the Investigator will be provided. Laboratory test values will be summarized over time.

Determination of Sample Size:

The planned total number of subjects enrolled into the Lead-In Period is approximately 334.

To estimate the odds ratio for the occurrence of flare with baseline MRI score based on historical MRI data, an effective sample size of 250 subjects in the dose tapering group will ensure a precision for the estimation with the width of 90% CI no more than 0.1 for an odds ratio 1.2, no more than 0.4 for an odds ratio 1.5, and no more than 1.0 for an odds ratio 1.8. Such sample size will also ensure a precision for the estimation of a continuous correlation coefficient ρ with the half width of 90% CI of ρ no more than 0.1 for a mild correlation coefficient 0.2, no more than 0.09 for a moderate correlation coefficient 0.4, and no more than 0.07 for a higher correlation with $\rho = 0.6$. Assuming a 30% flare rate, this sample size will provide the precision that the 2-sided 90% CI of the flare rate has a half width no more than 5%.

Under a 5:1 randomization ratio (dose tapering vs. withdrawal), a total of 300 subjects will be randomized. Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 334 subjects will need to be enrolled into the Lead-In Period.

Has been changed to read:

AbbVie Inc.	Protocol Number: M14-500
Name of Study Drug: Adalimumab	Phase of Development: 4
Name of Active Ingredient: Adalimumab	Date of Protocol Synopsis: 25 February 2016
<p>Protocol Title: A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected via Imaging TEchniques Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA)</p>	
<p>Objectives: The primary objective is to investigate the association between residual disease activity at Baseline as detected by magnetic resonance imaging (MRI) and the occurrence of flares in RA subjects randomized to an adalimumab dose tapering regimen controlled by adalimumab withdrawal. The Secondary Objectives are:</p> <ul style="list-style-type: none"> • To assess the occurrence and severity of flares and the time to flare in both taper and withdrawal arms. • To investigate the association between Double-Blind Baseline (dbBaseline) subject demographic and disease characteristics and the occurrence of flares. • To investigate the association between dbBaseline adalimumab trough concentrations and the occurrence of flares. • To evaluate the effectiveness of rescue therapy with open-label adalimumab 40 mg every other week (eow) over 16 weeks in subjects experiencing a flare. • To assess the change in rheumatoid arthritis MRI scoring system (RAMRIS) scores from Baseline to Final visit in the taper, withdrawal and Open-Label Rescue Arms. • To investigate the MRI-flare associations in sub-groups of subjects who meet additional clinical remission criteria at dbBaseline including simplified disease activity index (SDAI) ≤ 3.3, clinical diseases activity index (CDAI) ≤ 2.8 and ACR/EULAR 2011 boolean-based remission, as well as to describe the course of disease and patient reported outcome (PRO) measures in the taper, withdrawal and Open-Label Rescue Arms overall and per dbBaseline subgroup. • To assess the rate of anti-adalimumab antibodies (AAA) positive subjects in the taper and withdrawal arms. <p>The study also has the following exploratory objectives:</p> <ul style="list-style-type: none"> • In the subgroup of subjects with a Baseline Ultrasound (US) assessment: <ul style="list-style-type: none"> ○ To investigate the association between Baseline ultrasound scores and the occurrence of flares. ○ To investigate the association between the Baseline ultrasound scores and Baseline MRI RAMRIS scores. ○ To describe the change in the ultrasound scores from Baseline to the time of the occurrence of a flare in the taper and withdrawal arms. • To investigate the association between biomarker values at dbBaseline (and their change over time) and the occurrence of flares. 	

<p>Investigators: Investigator information is on file at AbbVie.</p>
<p>Study Sites: Approximately 72 sites in North America, Europe and Australia</p>
<p>Study Population: Subjects age ≥ 18 years diagnosed with RA, on a stable dose of adalimumab 40 mg subcutaneously (sc) eow (for ≥ 12 months prior to Week 0 Visit) in combination with methotrexate (MTX) (at stable dose for ≥ 12 weeks prior to Week 0 Visit) or if not on MTX, another allowed conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) at stable dose or no csDMARDs for ≥ 12 weeks prior to Week 0 Visit) and in documented clinical remission, defined as DAS28 erythrocyte sedimentation rate (ESR) < 2.6 or DAS28 c-reactive protein (CRP) < 2.6, for ≥ 6 months prior to the Screening Visit and DAS28 (ESR) < 2.6 at the Screening Visit. Patients who are not treated with concomitant stable dose of MTX are limited to a maximum of 20% of the study population.</p>
<p>Number of Subjects to be Enrolled: Approximately 200</p>
<p>Methodology: This is a Phase 4, multicenter, randomized, double-blind, parallel-group study in subjects with RA who are in stable clinical remission defined as DAS28 (ESR) or DAS28 (CRP) < 2.6 for at least 6 months prior to the Screening Visit. Though the cut-off for clinical remission of DAS28 (CRP) may not be equivalent to the DAS (ESR), in clinical practice both are frequently used to define remission as < 2.6. Both ESR or CRP and 4 or 3 (when Patient Global Assessment [PGA] is not available) variables DAS28 will be allowed for the purposes of identifying subjects for Screening; however, throughout the study clinical remission will be defined by the more stringent 4 variables DAS28 (ESR) < 2.6 criteria. At Screening, only subjects with confirmed 4 variables DAS28 (ESR) < 2.6 will be considered for inclusion in the study. The study activities will start with a Screening Period of up to 28 days to confirm inclusion/exclusion criteria including a DAS28 (ESR) assessment of < 2.6. Subjects who have signed the Informed Consent and who fulfill all Screening criteria will enter the study. The study starts with a 4-week Lead-In Open-Label (OL) Period during which stable DAS28 (ESR) clinical remission in 2 assessments 4 weeks apart will be confirmed. Subjects will receive adalimumab 40 mg sc eow starting at the Week 0 Visit of the Lead-In Period; this will be approximately 2 weeks after their last commercial Humira[®]. If needed for study procedures completion or injection scheduling adjustment, the lead-in period can be extended for up to 2 more weeks in which case the Week 4 Visit study procedures will occur up to 6 weeks after the Week 0 Visit. At Week 4, the end of the Lead-In Period, subjects will have a dbBaseline visit. Subjects must have a confirmed DAS28 (ESR) remission at two time points in order to be randomized: 1. DAS28 (ESR) < 2.6 at the Lead-In Period Week 0 2. DAS28 (ESR) < 2.6 at the dbBaseline visit Week 4 Subjects who meet the remission criteria will be randomized (5:1) to one of two double-blind arms and followed for additional 36 weeks in the Double-Blind Period: 1. A reduced frequency of adalimumab 40 mg sc every 3 weeks (q3wks): taper arm, or 2. Adalimumab placebo sc q3wks: withdrawal arm.</p>

Methodology (Continued):

All subjects who are taking concomitant MTX (any dose oral, subcutaneous [sc] or intramuscular [im]) and/or other csDMARDs at a stable dose for at least 12 weeks prior to Week 0 Visit will maintain the regimen throughout the Lead-In and Double-Blind Periods of study. Subjects who have not been taking any csDMARDs for at least 12 weeks prior to the Week 0 Visit, will also maintain this regimen throughout the Lead-In and Double-Blind Periods of study.

Any other allowed RA concomitant medications should also be kept stable throughout the Lead-In and Double-Blind Periods of the study; these medications and MTX will be received by local prescriptions.

During the Double-Blind Period, subjects will be evaluated every 6 weeks for efficacy, including detection of flares, PROs, safety and laboratory assessments at scheduled visits on: Weeks 4, 10, 16, 22, 28, 34 and 40 (Final visit).

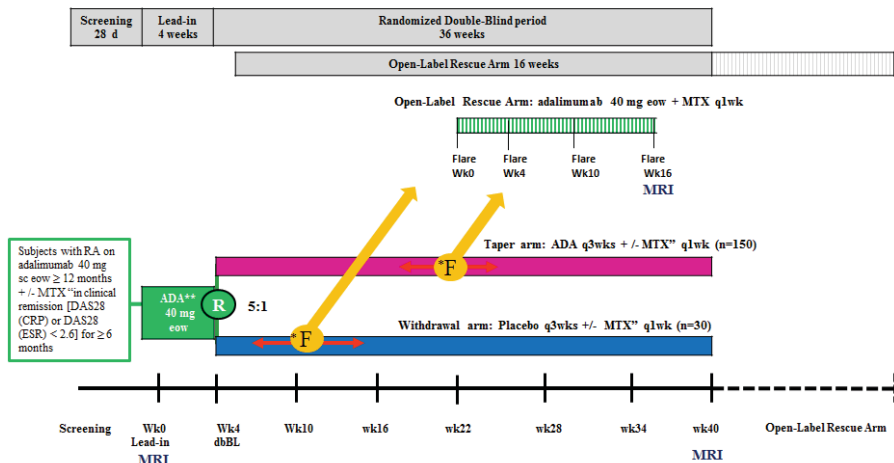
Other unscheduled visits will occur in the suspected event of a flare. During the interval between scheduled visits, subjects will be asked to contact their physicians in case of feeling their disease is worsening: an unscheduled visit will be performed within 2 weeks of contact with the site to assess if subjects are experiencing a flare.

Subjects with a confirmed flare (defined as an increase from dbBaseline in DAS28 [ESR] of > 0.6 AND a DAS28 [ESR] > 2.6, OR an increase in DAS28 (ESR) of ≥ 1.2 irrespective of the resulting DAS28 [ESR]) at any time point (at a scheduled or unscheduled visit) will undergo Flare Week 0 visit procedures and will be immediately switched to an Open-label rescue arm initiating adalimumab 40 mg eow rescue therapy.

In the Open-Label Rescue Arm, subjects will be further evaluated at Flare Weeks 4, 10 and 16 for efficacy, PROs, safety and laboratory assessments.

During this period, further treatment escalation/change will be allowed based on the Investigator's medical judgment. Any treatments escalation/change will be documented. At Flare Week 0, all subjects will be requested to initiate weekly at home self-assessment of their RA disease activity by using Routine Assessment of Patient Index Data (RAPID)-3 questionnaires until Week 16.

See study schematic below:



* Flare at any time point; Flare defined as: DAS28 (ESR) ≥ 2.6 AND an increase in DAS by >0.6 OR an increase in DAS28 (ESR) by ≥ 1.2 from dbBaseline irrespective of DAS28(ESR); Subjects who flare at any time during the randomized Double-Blind period will be switched to OL ADA 40 mg eow and continue in the Open-Label Rescue Arm for 16 weeks up to a maximum study duration of 36 weeks.
** ADA = adalimumab
*** at least 80 % of patients in combination treatment with stable MTX ≥ 12 weeks; up to 20% on stable other csDMARDs or adalimumab monotherapy ≥ 12 weeks

Methodology (Continued):

A high-field contrast MRI of the most affected hand (2nd to 5th MCP) and wrist will be performed on all subjects during the Lead-In Period (prior to the dbBaseline visit) and at Final/Early Termination Visit. If both sides are considered equally affected, the MRI of the dominant hand (2nd to 5th MCP) and wrist will be performed.

The acquired MRI images will be centrally read and Investigators will be blinded to the results. Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.

In sites that meet pre-specified ultrasound requirements and who wish to participate in the ultrasound portion of the study, subjects will undergo US assessment using Gray Scale Ultrasonography (GSUS) and Power Doppler Ultrasonography (PDUS) consisting of a systematic longitudinal and transverse multiplanar examination of 46 joints and 18 tendon/tendon compartment during Lead-In or at dbBaseline Visit prior to randomization and at the Flare Week 0 Visit (if applicable). US will be performed and assessed by local Ultrasonographer independent of the clinical assessor who will be blinded to the US scores.

Pharmacokinetics (PK) and immunogenicity will be assessed based on serum adalimumab trough concentrations and serum anti-adalimumab antibodies (AAA), respectively. Blood samples for adalimumab concentrations and measurements of AAA will be taken prior to dosing at dbBaseline (Week 4), at Weeks 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable).

A panel of inflammatory biomarkers: matrix metalloproteinase 3 (MMP3), Collagen neo-epitope (C1M), Type III collagen neo-epitope (C3M), Matrix metalloproteinase-mediated c-reactive protein (CRPM), Matrix metalloproteinase-degraded citrullinated vimentin (VICM), Serum amyloid-associated protein (SAA), Interleucin-6 (IL-6), Chemokine (C-X-C motif) ligand 10 CXCL10 and CXCL13 will be assessed at dbBaseline (Week 4), Weeks 10, 16, 28, 40 or at Early Termination, Flare Weeks 0, 4 and 16 (if applicable) on blood samples taken prior to dosing. At the time of analysis, other potential biomarkers identified as adding value to predict flare in this patient population may be included.

Additional optional samples for future biomarker research will be collected.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- Male or female subjects ≥ 18 years of age.
- Subject has a diagnosis of RA as defined by the 1987 revised ACR classification criteria and/or the ACR/EULAR 2010 classification criteria (any duration since diagnosis).
- Subject must meet the following criteria:
 - Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Week 0 Visit;
 - Must be treated with concomitant MTX at a stable dose (oral, sc or im at any dose) for at least 12 weeks prior to Week 0 Visit or if not on MTX, must be treated with other allowed csDMARDs at stable dose for at least 12 weeks prior to Week 0 Visit or if not treated with csDMARDs must maintain this regimen for at least 12 weeks prior to Week 0 Visit.
- Subject must be in sustained clinical remission based on the following:
 - At least one documented 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) < 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
 - 4 variables DAS28 (ESR) assessed at Screening < 2.6 , with all components including ESR assessed at Screening.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

- If subjects are receiving concomitant allowed csDMARDs (in addition or not to MTX) the dose must be stable for at least 12 weeks prior to the Week 0 Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
- If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to the Week 0 Visit.
- If subjects are receiving concomitant non-steroidal anti-inflammatory drugs (NSAIDs), tramadol or other equivalent opioids and/or non-opioid analgesics, the dose and/or therapeutic scheme must be stable for at least 4 weeks prior to the Week 0 Visit.
- Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol.

Main Exclusion:

- Any 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit ≥ 2.6 .
- Subject is on an additional concomitant biological disease-modifying anti-rheumatic drug (bDMARD) (including but not limited to abatacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab or tocilizumab).
- Subject has been treated with intra-articular or parenteral corticosteroids within the last 4 weeks before Screening.
- Subject has undergone joint surgery within 12 weeks of Screening (at joints to be assessed by MRI and/or ultrasound).
- Subject has a medical condition precluding an MRI (e.g., magnetic activated implanted devices – cardiac pace-maker, insulin pump, neurostimulators, etc. and metallic devices or fragments or clips in the eye, brain or spinal canal and in the hand/wrist undergoing MRI).
- Subject has a medical condition precluding a contrast MRI with gadolinium (e.g., nephrogenic systemic fibrosis, previous anaphylactic/anaphylactoid reaction to gadolinium containing contrast agent, pregnancy or breastfeeding, severe renal insufficiency with an estimated Glomerular Filtration Rate [eGFR] below 30 mL/min/1.73 m² at Screening, hepato-renal syndrome, severe chronic liver function impairment).
- Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Screening Visit.

Investigational Product:	Adalimumab
Dose:	Lead-In Period: Adalimumab 40 mg OL eow for 4 weeks Double-Blind Period: Adalimumab 40 mg q3wks for 36 weeks Open-Label Rescue Arm: Adalimumab 40 mg OL eow for a minimum of 16 weeks
Mode of Administration:	Subcutaneously (SC) pre-filled syringe

Reference Therapy:	Placebo for the Double-Blind Period
Dose:	0.8 ml q3wks
Mode of Administration:	Subcutaneously (SC) pre-filled syringe
Duration of Treatment:	<p>The duration of treatment will include a 4-week Lead-In Period (adalimumab 40 mg sc eow) followed by a 36-week, randomized, Double-Blind Period with 2 arms: taper arm (adalimumab 40 mg sc q3wks) controlled by withdrawal matching placebo arm. Open-Label Rescue Arm (adalimumab 40 mg sc eow) will be provided for 16 weeks (if applicable). Therefore, the total duration of the study is 40 or 56 weeks (if applicable).</p>
Criteria for Evaluation:	<p>Efficacy:</p> <p>Primary Efficacy Variables</p> <ul style="list-style-type: none"> The primary explanatory variables are the Baseline hand and wrist synovitis and bone marrow edema (BME) RAMRIS scores as well as a composite of both and the dependent variable is the occurrence of flare up to Week 40 in the tapering arm. <p>Secondary Variables</p> <ul style="list-style-type: none"> Time to flare Flare severity Proportion of subjects experiencing a flare Subject demographics and clinical disease characteristics at dbBaseline, including <ul style="list-style-type: none"> Smoking status, co-morbidities, anti-citrullinated peptide antibody (ACPA) status, Rheumatoid Factor (RF) status, disease duration, previous treatment with conventional synthetic Disease Modifying Anti-rheumatic Drugs (csDMARDs) or biologic Disease Modifying Anti-rheumatic Drugs (bDMARDs) or both, duration of adalimumab therapy, remission duration, disease activity, c-reactive protein (CRP) and Health Assessment Questionnaire (HAQ) score Proportion of subjects who regain clinical remission (defined as DAS28 [ESR] < 2.6 and defined as DAS28 (ESR) decrease > 1.2 if DAS28 [ESR] was less than 2.6 at flare) in the Open-Label Rescue Arm over time Time to regain clinical remission in the Open-Label Rescue Arm Proportion of subjects with low disease activity (defined as DAS28 [ESR] < 3.2) in the Open-Label Rescue Arm over time Change from Baseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI: DAS28 [ESR] < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8) throughout the study Change from dbBaseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores Change from Baseline in DAS28 (ESR), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Proportion of subjects maintaining clinical remission (defined by DAS, SDAI and CDAI: DAS28 [ESR] < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8) throughout the study

Criteria for Evaluation (Continued):

Efficacy (Continued):

Secondary Variables (Continued)

- Change from dbBaseline to Week 40 or final Visit in MRI synovitis, BME and erosions RAMRIS scores
- Change from Baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) over time
- Proportion of subjects with HAQ-DI normal (HAQ-DI \leq 0.5) at dbBaseline and at Week 40
- Change from dbBaseline in RAPID 3 scores assessed during Visits
- Change from Flare Week 0 in RAPID 3 at home assessments
- Change from dbBaseline in Swollen Joint Count (both 28 and 66 joints)
- Change from dbBaseline in Tender joint Count (both 28 and 68 joints)
- Change from dbBaseline in Patient's Global Assessment of Disease activity
- Change from dbBaseline in Patient's Global Assessment of RA pain
- Change from dbBaseline in Physician's Global Assessment of Disease activity
- Change from dbBaseline in morning stiffness assessment
- Change from dbBaseline in Sleep disturbance assessment
- Change from dbBaseline in Treatment Satisfaction Questionnaire for Medication (TSQM)
- Change from dbBaseline in Work Productivity and Activity Impairment (WPAI)
- Change from dbBaseline in Short Form-36 (SF-36)
- Change from dbBaseline in Functional Assessment of Chronic Illness Therapy – fatigue (FACIT-fatigue)
- Change from dbBaseline in CRP
- Change from dbBaseline in ESR

Exploratory Variables

- Baseline and change from Baseline to the time of flare in PDUS and GSUS individual and composite scores of synovitis, synovial hypertrophy and tenosynovitis
- dbBaseline and change from dbBaseline on biomarker values (MMP3, SAA, C1M, C3M, CRPM, VICM, IL-6, CXCL10, CXCL13)

Pharmacokinetics:

- Adalimumab concentrations measurement dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4 and 16 (if applicable)
- AAA measurement at dbBaseline (Week 4), Week 10, 16, 28, 40 and at Early Termination, Flare Weeks 0, 4, 10 and 16 (if applicable)

Interim Analysis for Double-Blind Baseline Characteristics:

There are few data describing patient disease characteristics, including markers of residual inflammation (such as sensitive imaging assessments and potential biomarkers) and drug levels in patients who are in sustained RA clinical remission on a stable treatment with a TNFi and MTX and/or with other csDMARDs(s) or in TNFi monotherapy. An interim analysis will be conducted to describe the dbBaseline characteristics of this RA population. It will be performed after the dbBaseline assessments and randomization of the entire study population have been completed.

Criteria for Evaluation (Continued):

Safety:

Screening assessments will include medical history, vital signs, physical examination, and clinical and laboratory tests. The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, physical examination (if required) and laboratory tests.

Statistical Methods:

Efficacy:

Analysis for Primary Objective:

The association between the occurrence of flares and Baseline MRI RAMRIS scores will be examined using logistic regression, which is deemed as the main analysis to address the primary objective. Additional analyses will be performed to assess this association using various statistical methods. Specifically, descriptive statistics of Baseline MRI RAMRIS scores will be provided for the two groups of subjects who flare and who do not flare, and the between-group difference in the mean scores will be computed together with a 90% confidence interval (CI). Linear regression will be used to model the relationship between the DAS28 (ESR) at flaring (or at end of study for subjects who do not flare) and the Baseline MRI RAMRIS scores. Receiver operating characteristic (ROC) curve approach will also be utilized to investigate the potential flare prediction criteria based on MRI RAMRIS scores. All model based analyses may adjust for dbBaseline clinical patient characteristics including disease duration, previous and concomitant treatment, etc. when appropriate.

Similar analysis will be conducted for RAMRIS synovitis scores, BME scores and the composite of both.

Analysis for Secondary Objectives:

Within the analyses to address the secondary objectives the association between dbBaseline disease characteristics and the occurrence of flares will be examined using similar analyses as for the primary objective. In addition, characterization of flares, response to rescue therapy in subjects experiencing a flare and the clinical and patient reported efficacy outcomes for all trial subjects will be analyzed accordingly.

Pharmacokinetic:

Adalimumab trough serum concentrations will be summarized by treatment arm at each time point using descriptive statistics. The association between dbBaseline adalimumab trough concentrations and the occurrence of flares will be assessed. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F) of adalimumab.

Immunogenicity:

AAA will be evaluated for each subject and each study arm, and rates of AAA positive subjects will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment emergent adverse events may be evaluated.

Statistical Methods (Continued):

Safety:

Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA) 17.0 dictionary, by system organ class and by causality to the study medication as assessed by the Investigator will be provided. Laboratory test values will be summarized over time.

Determination of Sample Size:

The planned total number of subjects enrolled into the Lead-In Period is approximately 200.

To estimate the odds ratio for the occurrence of flare with baseline MRI score based on historical MRI data, an effective sample size of 150 subjects in the dose tapering group will ensure a precision for the estimation with the width of 90% CI no more than 0.03 for an odds ratio 1.03, no more than 0.07 for an odds ratio 1.1, and no more than 0.14 for an odds ratio 1.2. Such sample size will also ensure a precision for the estimation of a correlation coefficient ρ with the width of 90% CI of ρ no more than 0.26 for a mild correlation coefficient 0.28, no more than 0.18 for a moderate correlation coefficient 0.55, and no more than 0.13 for a higher correlation with $\rho = 0.67$. Assuming a 30% flare rate, this sample size will provide the precision that the 2-sided 90% CI of the flare rate has a half width no more than 6%.

Under a 5:1 randomization ratio (dose tapering vs. withdrawal), a total of 180 subjects will be randomized. Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 200 subjects will need to be enrolled into the Lead-In Period.

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

Add: "CI"

CI Confidence Interval

Section 3.3 Rationale for the Study

Sixth paragraph, last sentence previously read:

Re-institution of normal dose/dosing regimen of TNFi in case of flares effectively providing patients the same level of disease control they had before?

Has been changed to read:

Is re-institution of normal dose/dosing regimen of TNFi in case of flares effectively providing patients the same level of disease control they had before?

Section 3.3.1 Additional Considerations on Key Study Parameters

Subsection Clinical Remission Defined by DAS28 < 2.6

Last paragraph previously read:

In this study, clinical remission for subjects inclusion in the study is defined by the potentially more stringent DAS28 (ESR) < 2.6; flare will be assessed based on DAS28(ESR) evaluation at any time point throughout the study (with ESR measured in the same visit). However, due to the common use of both scores in clinical practice, for the purpose of identifying subjects for Screening, both DAS28 (ESR) and (CRP) documented as being lower than 2.6 for at least 6 months prior to screening will be accepted. At Screening only, subjects with DAS28 (ESR) < 2.6 may be enrolled.

Has been changed to read:

In clinical practice it's relatively frequent to use the also validated 3 variables DAS28³² or instead of the most widely used DAS28 4 variables due to difficulties on getting documented patient global assessment (PGA) in a Visual Analogue Scale (VAS). Moreover, a recent study has shown that despite the existence of individual patient baseline differences prior to treatment with TNFi, after 12 weeks of TNFi and particularly for the lower range the 3 and 4 variables DAS28 (CRP).scores were similarly sensitive to change, highly correlated and the mean inter-score difference was very small.³³ Accordingly, for the purpose of identifying subjects on stable clinical remission for ≥ 6 months for Screening, both DAS28 (ESR) and (CRP) 4 or 3 (when PGA is not available) variables documented as being lower than 2.6 for at least 6 months prior to screening will be accepted. However, at Screening, only subjects with 4 variables DAS28 (ESR) < 2.6 may be enrolled and throughout the study clinical remission is defined by the 4 variables DAS28 (ESR) < 2.6. Flare will be assessed based on DAS28 (ESR) evaluation at any time point throughout the study (with ESR measured in the same visit).

Concomitant Treatments for RA

The 2013 EULAR recommendations update propose that in RA patients who are in stable clinical remission particularly if also treated with concomitant csDMARDs(s) tapering a

bDMARD is an option; the updated 2015 ACR guidelines also consider tapering RA treatments as an option for such a patient population. Both treatment recommendations acknowledge that more data on tapering is needed as part of a research agenda.

It is the aim of this study to assess, in subjects treated in real life clinical practice conditions who have DAS28 < 2.6, if imaging-detected sub-clinical inflammation (and disease, patient and treatment patterns as well as adalimumab drug level characteristics) brings an additional benefit in predicting and informing clinicians about who has a higher risk of flare while treated with a reduced dose of adalimumab.

As this study goal is to include patients as treated in routine clinical practice, the patient population must be in line with both treatment recommendations and clinical practice. Accumulated data from registries and other real world evidence, such as CORRONA,³⁴ US healthcare insurance claims database,³⁵ BSRBR,³⁶ RABBIT,³⁷ Nor-DMARD³⁸ and ARTIS³⁹ are showing that around 30% – 34% of patients being treated with bDMARDs including TNFi are on monotherapy even if at initiation of the bDMARD the vast majority of patients were on combination therapy.⁴⁰ As such this study will include mainly patients who are in stable remission for more than 6 months as assessed by DAS28 < 2.6 and after at least 1 year of treatment with adalimumab with concomitant MTX for at least the last 12 weeks prior to inclusion; in order to be in line with the current clinical practice up to 20% of the study patient population may be composed of subjects who are not treated with concomitant stable MTX but instead are treated with other than MTX allowed csDMARDs or not treated with a csDMARD as long as this treatment regimen is stable for at least 12 weeks prior to Week 0.

Section 3.6 Benefits and Risks

Third paragraph, last sentence previously read:

All subjects will maintain a stable dose of MTX (any dose; oral or sc) and additional RA concomitant medication if deemed necessary before enrollment into the study.

Has been changed to read:

Subjects will maintain a stable dose of MTX (any dose; oral, sc or im) and/or of any other additional concomitant RA medication as taken before enrollment into the study.

Section 4.0 Study Objectives

Second paragraph, sixth bullet previously read:

To describe the course of disease using clinical and patient reported outcomes (PROs) measures in the taper, withdrawal and Open-Label Rescue Arms.

Has been changed to read:

To investigate the MRI-flare associations in sub-groups of subjects who meet additional clinical remission criteria at dbBaseline including simplified disease activity index (SDAI) ≤ 3.3 , clinical diseases activity index (CDAI) ≤ 2.8 and ACR/EULAR 2011 boolean-based remission, as well as to describe the course of disease and patient reported outcome (PRO) measures in the taper, withdrawal and Open-Label Rescue Arms overall and per dbBaseline subgroup.

Section 4.0 Study Objectives

Last paragraph, bullet list read:

- In the subgroup of subjects with a dbBaseline Ultrasound (US) assessment:
 - To investigate the association between dbBaseline ultrasound scores and the occurrence of RA flares.
 - To investigate the association between the dbBaseline ultrasound scores and Baseline MRI RAMRIS scores.
 - To describe the change in the ultrasound scores from dbBaseline to the time of RA flare in the taper and withdrawal arms.
 - To investigate the association between biomarker values at dbBaseline (or their change over time) and the occurrence of RA flares.

Has been changed to read:

- In the subgroup of subjects with a Baseline Ultrasound (US) assessment:
 - To investigate the association between Baseline ultrasound scores and the occurrence of RA flares.
 - To investigate the association between the Baseline ultrasound scores and Baseline MRI RAMRIS scores.
 - To describe the change in the ultrasound scores from Baseline to the time of RA flare in the taper and withdrawal arms.
- To investigate the association between biomarker values at dbBaseline (or their change over time) and the occurrence of flares.

Section 5.1 Overall Study Design and Plan: Description

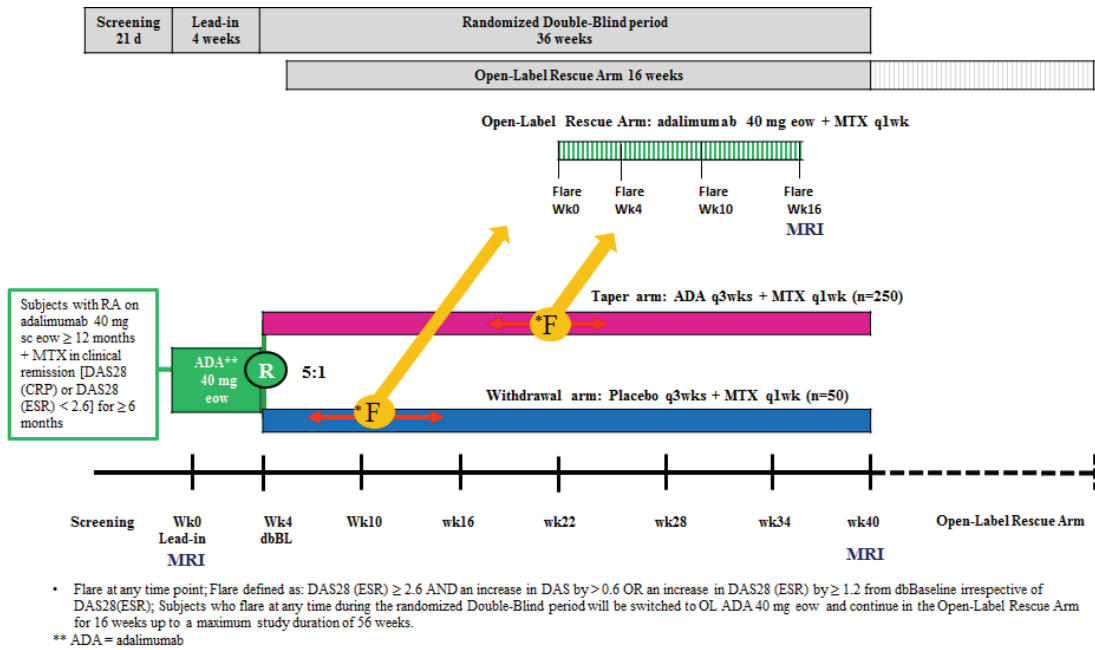
First paragraph, last paragraph previously read:

The study duration will include a Screening period of up to 21 days, a 4-week Lead-In Period with open-label 40 mg adalimumab eow and a 36-week Double-Blind Period with 40 mg adalimumab/placebo q3wks; subjects who experience a flare at any time will enter a Rescue Arm and will be followed for 16 weeks.

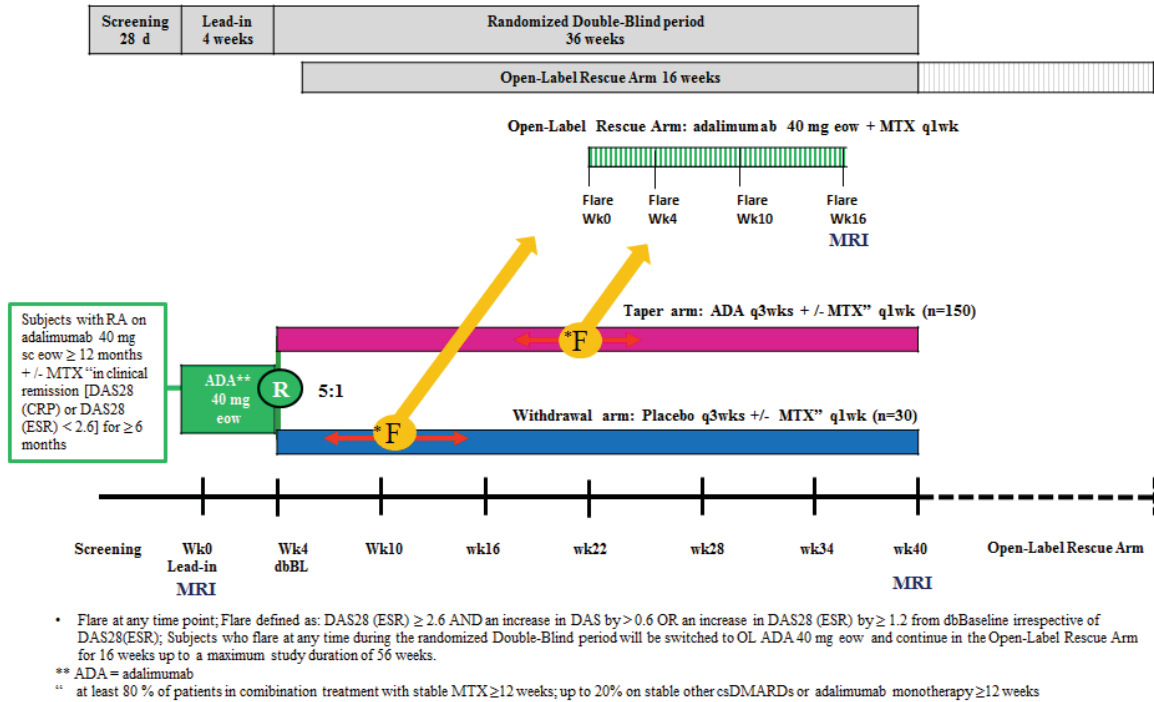
Has been changed to read:

The study duration will include a Screening period of up to 28 days, a 4-week Lead-In Period with open-label 40 mg adalimumab eow and a 36-week Double-Blind Period with 40 mg adalimumab/placebo q3wks; subjects who experience a flare at any time will enter a Rescue Arm and will be followed for 16 weeks.

Figure 1. Study Design Schematic
Previously read:



Has been changed to read:



Section 5.1 Overall Study Design and Plan: Description

Subsection Screening Period

Subsection title and first and second paragraph previously read:

Screening Period

At the Screening Visit, prior to the Lead-In Period, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the Screening procedures outlined in Table 1.

The target population for the study consists of RA subjects on adalimumab treatment for at least 12 months and in stable clinical remission, as defined by a DAS28 (CRP) or DAS28 (ESR) $<$ 2.6 for at least 6 months prior to the Screening Visit, in combination with MTX (at a stable dose for \geq 12 weeks prior to Screening Visit). Subjects with a documented DAS28 (CRP) or (ESR) $<$ 2.6 (or availability of all the components that

allow for calculation of a DAS28 score) at least 6 months prior to Screening Visit may be screened. However, for enrollment and throughout the study clinical remission will be defined by DAS28 (ESR) < 2.6 criteria.

Has been changed to read:

Screening Period (up to 28 days):

At the Screening Visit, prior to the Lead-In Period, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the Screening procedures outlined in [Table 1](#). The Screening period may be exceptionally extended beyond 28 days upon justification and further consultation with Study Designated Physician. The target population for the study consists of RA subjects on adalimumab treatment for at least 12 months and in stable clinical remission, as defined by a 4 or 3 (whenever PGA is not available) variables DAS28 (CRP) or DAS28 (ESR) < 2.6 for at least 6 months prior to the Screening Visit, in combination with MTX (at a stable dose for ≥ 12 weeks prior to Week 0 Visit) or if not on MTX, in other allowed csDMARDs at a stable dose or not treated with a csDMARD for ≥ 12 weeks prior to Week 0 Visit. Subjects with a documented DAS28 (CRP) or (ESR) < 2.6 (or availability of the 4 or at least 3 components that allow for calculation of a DAS28 score) at least 6 months prior to Screening Visit may be screened. However, for enrollment and throughout the study clinical remission will be defined by 4 variables DAS28 (ESR) < 2.6 criteria.

Section 5.1 Overall Study Design and Plan: Description

Subsection Screening Period

Third paragraph, last sentence previously read:

Confirmation of a DAS28 (ESR) < 2.6 assessed at the Screening Visit is required prior to subject inclusion into the Lead-In Period.

Has been changed to read:

Confirmation of a DAS28 (ESR) < 2.6 assessed at the Screening and at the Week 0 Visit is required prior to subject inclusion into the Lead-In Period.

Section 5.1 Overall Study Design and Plan: Description

Subsection Screening Period

Last paragraph

Add: new last sentence

If the re-screening visit is occurring within 4 weeks of last screening some other procedures may not be required upon discussion and agreement with Study Designated Physician.

Section 5.1 Overall Study Design and Plan: Description

Subsection Lead-In Period 4 Weeks:

Previously read:

Subjects who fulfill all Screening criteria will enter the study with a 4-week Lead-In OL Period: subjects will receive adalimumab 40 mg sc eow starting at Week 0 of the Lead-In Period. Week 0 will occur 2 weeks after the subject's last dose of commercial Humira[®] (± 2 days) to keep in line with eow dosing; the second injection will be given 14 days thereafter (± 2 days). Subjects must undergo an MRI scan of the most affected or of the dominant hand (2nd to 5th MCP) and wrist (if both sides are considered equally affected) during the 4-week Lead-In Period.

MRI images will be read centrally. Further details regarding MRI requirements, procedures and central reading will be provided in an MRI manual. The assessors will be blinded to the clinical assessments and the clinical Investigator will be blinded to the MRI assessments. The dbBaseline Visit and randomization are not dependent on the results or report of the central reader. Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.

Sites will be asked at study-start if they want to participate and if they qualify for the optional US assessment, according to requirement described in Appendix N and in the US

manual. Sites that participate in US assessments will need to nominate a qualified Ultrasonographer to perform and locally assess the US; there will not be a central reading of the US images. The Ultrasonographer will be blinded to the clinical assessments and the clinical Investigator will be blinded to the ultrasound assessments.

Has been changed to read:

Subjects who fulfill all Screening criteria will enter the study with a 4-week Lead-In OL Period: subjects will receive adalimumab 40 mg sc eow starting at Week 0 of the Lead-In Period. Week 0 will occur 2 weeks after the subject's last dose of commercial Humira[®] (± 2 days) to keep in line with eow dosing. At the Week 0 visit subjects will undergo the corresponding procedures as outlined in [Table 1](#) including DAS28 (ESR) assessment to confirm remission using the ESR result from the same day of the visit. If the subject enrollment is confirmed at the Week 0 visit, the subject will stop commercial Humira[®] and initiate adalimumab investigational product open-label sc. The first sc injection will be administered at the site at the end of the visit; the second injection will be given 14 days thereafter (± 3 days) and every other week (± 3 days) until Week 4 dbBaseline Visit. If needed the subject may be assisted by the study team for the self-injection of the syringe. Subjects must undergo a high-field contrast MRI scan of the most affected hand (2nd to 5th MCP) and wrist during the Lead-In Period. If both sides are considered equally affected the MRI of the dominant hand (2nd to 5th MCP) and wrist will be performed.

MRI images will be read centrally. Further details regarding MRI requirements, procedures and central reading will be provided in an MRI manual. The assessors will be blinded to the clinical assessments and the clinical Investigator will be blinded to the MRI assessments performed centrally. A local report for safety reasons on urgent and RA inflammation related findings other than RA may be viewed by the investigator. The dbBaseline Visit and randomization are not dependent on the results or report of the central reader. **Subjects should be randomized only when the MRI has been confirmed to be received and complete by Central Imaging.**

Sites will be asked at study-start if they want to participate and if they qualify for the optional US assessment, according to requirement described in [Appendix N](#) and in the US manual. Sites that participate in US assessments will need to nominate a qualified Ultrasonographer to perform and locally assess the US during the Lead-In period or at the dbBaseline Visit; there will not be a central reading of the US images. The Ultrasonographer will be blinded to the clinical assessments and the clinical Investigator will be blinded to the ultrasound assessments.

If needed for procedural compliance (e.g., to allow MRI and its certification, for injection scheduling adjustment), the lead-in period can be extended up to 2 more weeks in which case the DAS28 (ESR) assessment and all the dbBaseline Week 4 Visit study procedures will occur up to 6 weeks after the Week 0 Visit. These cases or other exceptions related with further extension of the Lead-in period should be discussed with the Study Designated Physician.

Section 5.1 Overall Study Design and Plan: Description

Subsection Double-Blind Period:

First paragraph

Add: new last sentence

At the Week 4 visit, if the subject does not meet the DAS28 (ESR) of < 2.6 or if the subject is unable to obtain confirmed and certified MRI scan images, the subject would need to be discontinued from the study at an Early Termination visit.

Section 5.1 Overall Study Design and Plan: Description

Subsection Double-Blind Period:

Second paragraph previously read:

Subjects with a confirmed DAS28 (ESR) of < 2.6 at the dbBaseline visit, and as such fulfilling confirmed DAS28 (ESR) remission at 2 time points: Day 1 of Lead-In and 4 weeks later at the dbBaseline visit, will be randomized in a 5:1 ratio to one of two double-blind arms and followed for an additional 36 weeks:

Has been changed to read:

Subjects with a confirmed DAS28 (ESR) of < 2.6 at the dbBaseline visit, and as such fulfilling confirmed DAS28 (ESR) remission at 2 time points: Day 1 of Lead-In and 4 weeks later (or, exceptionally later) at the dbBaseline visit, will be randomized in a 5:1 ratio to one of two double-blind arms and followed for an additional 36 weeks:

Section 5.1 Overall Study Design and Plan: Description

Subsection Double-Blind Period:

Fourth paragraph previously read:

At each scheduled visit subjects will undergo the corresponding procedures as outlined in Table 1. The initial assessments at each of these visits must include ESR assessment and the clinical DAS28 components; if the calculated DAS score meets flare criteria described below, the visit then becomes a Flare Week 0 Visit; and the stipulated procedures are completed.

Has been changed to read:

At each scheduled visit during the double-blind period subjects will undergo the corresponding procedures as outlined in [Table 1](#). The initial assessments at each of these visits must include ESR assessment except if the blood puncture for this procedure is very painful (in which case subjects should first fulfill the patient questionnaires); if the calculated DAS score meets flare criteria described below, the visit then becomes a Flare Week 0 Visit; and the stipulated procedures are completed.

Section 5.1 Overall Study Design and Plan: Description

Subsection Double-Blind Period:

Fifth paragraph, first sentence previously read:

Visits should aim to be scheduled in line with the injection date (± 2 days); in this case, subjects should be reminded not to take their injection prior to coming for the visit.

Has been changed to read:

Visits, including the dbBaseline Visit should aim to be scheduled in line with the injection date (± 3 days); in this case, subjects should be reminded not to take their scheduled injection prior to coming for the visit.

Section 5.1 Overall Study Design and Plan: Description

Subsection Flare at Scheduled Visit:

Last paragraph, first sentence previously read:

At the Flare Week 0 Visit, subjects will undergo further study procedures as described in Table 1 under Scheduled/Unscheduled Flare Week 0 Visit and will be switched to Open-Label Rescue Arm starting with the first OL injection of adalimumab 40 mg sc at the visit.

Has been changed to read:

At the Flare Week 0 Visit, subjects will undergo further study procedures as described in [Table 1](#) under Scheduled/Unscheduled Flare Week 0 Visit and will be switched to Open-Label Rescue Arm starting with the first OL injection of adalimumab 40 mg sc at the end of the visit.

Section 5.1 Overall Study Design and Plan: Description

Subsection Unscheduled Visit:

First paragraph, second sentence previously read:

If a subject contacts the site due to possible worsening of RA, an unscheduled visit to confirm his/her clinical status within 15 days of contact with the site.

Has been changed to read:

If a subject contacts the site due to possible worsening of RA, an unscheduled visit to confirm his/her clinical status within 2 weeks of contact with the site.

Section 5.1 Overall Study Design and Plan: Description

Subsection Flare at Unscheduled Visit:

Previously read:

If during a scheduled visit a flare (defined by DAS28 [ESR] > 2.6 AND an increase from dbBaseline in DAS28 [ESR] > 0.6 or increase of DAS28 [ESR] \geq 1.2 from dbBaseline DAS28 [ESR] score irrespective of DAS28 [ESR]) is confirmed, the regular visit will then turn into a Flare Week 0 Visit.

Has been changed to read:

At the Flare Week 0 visit subjects will undergo further study procedures as described in [Table 1](#) under Scheduled/Unscheduled Flare Week 0 Visit and will be switched to the Open Label Rescue Arm starting with the first adalimumab 40 mg sc OL injection at the end of the visit if last study drug injection has occurred more than 1 day ago. If not, OL adalimumab 40 mg will be provided for at home sc injection starting the next day.

Section 5.1 Overall Study Design and Plan: Description

Subsection Open-Label Rescue Arm

First paragraph

Add: new last sentence

After the first OL injection, adalimumab 40 mg will be administered sc eow. Subjects will be given RAPID 3 questionnaires (for self-assessment of disease activity) for weekly completion to be returned at every visit until the Flare Week 16 Visit.

Section 5.1 Overall Study Design and Plan: Description

Subsection Open-Label Rescue Arm

Fourth paragraph, third bullet previously read:

Corticosteroids (a dose up to a maximum of 15 mg oral prednisolone or equivalent/day and up to 3 injections intra-articular (i.a.) within the follow-up period of 16 weeks)

Has been changed to read:

- Corticosteroids (a dose up to a maximum of 15 mg oral prednisolone or equivalent/day and/or up to 3 injections intra-articular (i.a.) within the follow-up period of 16 weeks)
- csDMARDs including MTX (initiation and/or dose or administration mode change) and excluding csDMARDs that are not allowed (e.g., azathioprine, cyclophosphamide, d-penicillamine)

Section 5.1 Overall Study Design and Plan: Description

Subsection Open-Label Rescue Arm

Fifth paragraph

Add: new last sentence

Four weeks after an i.a. injection, joints must be again evaluated and included in the scores.

Section 5.1 Overall Study Design and Plan: Description

Subsection Open-Label Rescue Arm

Last paragraph previously read:

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination Visit. Subjects who prematurely discontinue should complete the procedures outlined for the Early Termination Visit in Table 1 as soon as possible after the last dose of study drug and preferably prior to the administration of new therapies. Subjects in the Open-Label Rescue Arm (adalimumab 40 mg sc eow) who continue on adalimumab therapy eow after the end of study participation will not be contacted for follow-up as any new adverse events should be reported through the mechanism used for all postmarketing adverse experiences. All other subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs.

Has been changed to read:

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination Visit.

Early Termination Visit

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects who prematurely discontinue while on the double blind and/or OL rescue period should complete the procedures outlined for the Early Termination/Final Visit in [Table 1](#) as soon as possible after the last dose of study drug and preferably prior to the administration of new therapies.

If subjects discontinue the study during the lead-in observational period from Week 0 up to Week 4, prior to randomization, a shortened Early Termination visit is required for: returning study material and drug, assess any safety/adverse events, collect reason for discontinuation. A 70-day follow-up call/visit will be required; the remainder of full Early Termination Visit study procedures can be completed per the investigator's discretion.

All subjects discontinuing the study will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events.

Section 5.2 Selection of Study Population

First paragraph, first and second sentence previously read:

Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 334 subjects will be enrolled into the Lead-In Period. The study is designed to randomize approximately 300 subjects in the Double-Blind Period to meet primary objective evaluation without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 200 subjects will be enrolled into the Lead-In Period. The study is designed to randomize approximately 180 subjects in the Double-Blind Period to meet primary objective evaluation without enrolling an undue number of subjects in alignment with ethical considerations.

Section 5.2.1 Inclusion Criteria

Criterion 3, 4, 5, 6, 7, and 8 previously read:

3. Subject must meet the following criteria:
 - Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Screening Visit
 - Must be treated with concomitant MTX in a stable dose (oral or sc at any dose) for at least 12 weeks prior to Screening Visit
4. Subject must be in sustained clinical remission based on the following:
 - At least one documented DAS28 (ESR) or DAS28 (CRP) < 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
 - DAS28 (ESR) assessed at Screening < 2.6 (with all components including ESR assessed at Screening).
5. If subjects are receiving concomitant csDMARDs in addition to MTX, the dose must be stable for at least 12 weeks prior to the Screening Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
6. If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to the Screening visit.
7. If subjects are receiving NSAIDs, the dose must be stable for at least 4 weeks prior to the Screening Visit.

8. If female subject, is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

Examples of approved methods of birth control include the following (see local informed consent for more detail):

- Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
- Hormonal contraceptives for 90 days prior to study drug administration;
- A vasectomized partner.

Has been changed to read:

3. Subject must meet the following criteria:
- Must be treated with adalimumab 40 mg sc eow for at least 12 months prior to Week 0 Visit;
 - Must be treated with concomitant MTX in a stable dose (oral, sc or im at any dose) for at least 12 weeks prior to Week 0 Visit or if not on MTX, must be treated with other allowed csDMARDs at stable dose for at least 12 weeks prior to Week 0 Visit or if not treated with csDMARDs must maintain this regimen for at least 12 weeks prior to Week 0 Visit.
4. Subject must be in sustained clinical remission based on the following:
- At least one documented 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) < 2.6 (or calculated based on documented components of the DAS28) in the patient chart 6 months or longer prior to the Screening Visit;
 - 4 variables DAS28 (ESR) assessed at Screening < 2.6 (with all components including ESR assessed at Screening).

5. If subjects are receiving allowed concomitant csDMARDs (in addition or not to MTX) the dose must be stable for at least 12 weeks prior to the Week 0 Visit (e.g., chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and/or leflunomide).
6. If subjects are receiving concomitant oral corticosteroids, prednisone or equivalent must be < 10 mg/day and the dose must be stable for at least 4 weeks prior to Week 0 visit.
7. If subjects are receiving concomitant NSAIDs, tramadol or other equivalent opioids and/or non-opioid analgesics the dose and/or therapeutic scheme must be stable for at least 4 weeks prior to the Week 0 Visit.
8. If female subject, is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.

Examples of approved methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly include the following (see local informed consent for more detail):

- Oral (except for low-dose progestin-only [lynestrenol and norethisteron]), injectable or implanted hormonal contraceptives started for 90 days prior to study drug administration;
- Intrauterine device (IUD);
- Intrauterine system (for example, progestin-releasing coil);
- A vasectomized male partner;
- Abstinence from vaginal intercourse (when in line with preferred and usual lifestyle of the subject)

Section 5.2.1 Inclusion Criteria

Criterion 11 previously read:

If these requirements are not met, subject will have a TB screening assessment: TB screening assessment is negative. If the subject has evidence of latent TB infection, the subject must initiate and complete at least the first 2 weeks (or per local guidelines whichever is longer) of TB prophylaxis prior to dbBaseline.

Has been changed to read:

11. Subject has a documented negative TB Screening assessment within 12 months prior to Screening Visit or if latent TB infection, subject has had a minimum of 2 weeks (or per local guidelines whichever is longer) of TB prophylaxis prior to treatment with adalimumab and had or is completing a full course of TB prophylaxis.

If these requirements are not met, subject must perform a TB screening assessment: subject has a negative TB screening assessment and if there is a strong suspicion of TB exposure the subject must be evaluated by a TB expert (Section 5.3.1.1). If the subject has evidence of latent TB infection, the subject must initiate and complete at least the first 2 weeks (or per local guidelines whichever is longer) of TB prophylaxis prior to Week 0.

Section 5.2.2 Exclusion Criteria

Criterion 1 previously read:

Any DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit ≥ 2.6 .

Has been changed to read:

Any 4 or 3 (if PGA is not available) variables DAS28 (ESR) or DAS28 (CRP) (or calculated based on documented components of the DAS28) assessed within 6 months prior to the Screening Visit ≥ 2.6 .

Section 5.2.2 Exclusion Criteria

Criterion 10 previously read:

Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (PML) (i.e., natalizumab [Tysabri[®]], rituximab [Rituxan[®]], or efalizumab [Raptiva[®]]) or prior treatment with azathioprine or cyclophosphamide.

Has been changed to read:

Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (PML) (i.e., natalizumab [Tysabri[®]], rituximab [Rituxan[®]], or efalizumab [Raptiva[®]]) or prior treatment with cyclophosphamide.

Section 5.2.3.1 Prior Therapy

Second, third and fourth paragraph previously read:

For each subject that is screened for the study, any other medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) taken 4 weeks prior to Week 0 Visit and throughout the end of the study must be recorded on the appropriate eCRF along with the date(s) of administration, reason for use, dosage, route and frequency.

Adalimumab use for ≥ 12 months prior to Screening is required per protocol; date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF.

MTX use at a stable dose (any dose; oral or sc) for ≥ 12 weeks prior to Screening is required per protocol; date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF.

Has been changed to read:

For each subject that is screened for the study, any other medication (including, but not limited to, over-the-counter medicines such as aspirin, antacids, vitamins, mineral supplements, and herbal preparations) taken 4 weeks prior to Week 0 Visit and throughout the end of the study must be recorded on the appropriate eCRF along with the date(s) of administration, reason for use, dosage, route and frequency.

Adalimumab use for ≥ 12 months prior to Week 0 Visit is required per protocol; date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF. A maximum of 2 non-consecutive adalimumab injections could have been skipped over the last 12 months but not during the 12 weeks prior to the Week 0 Visit. Reason(s) for a previously missed dose should be documented and cannot be due to an intentional tapering of medication (e.g., infection, surgery, lack of medication). Also there must be no evidence of $\text{DAS28} \geq 2.6$ during the last 6 months prior to screening as per exclusion criteria. A discussion with Study Designated Physician is recommended. MTX use at a stable dose (any dose; oral, sc or im) for ≥ 12 weeks prior to Week 0 Visit is required for at least 80% of subjects recruited; for those subjects on concomitant MTX, date of first use, dosage, maximum dosage and reason for use as well as RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF. A decrease in the dose of MTX due to an event of tolerability (or other safety) related with MTX is allowed during the 12 weeks period prior to the Week 0 Visit and throughout the study as long as well documented.

Subjects who are not taking MTX in a stable dose for ≥ 12 weeks prior to Week 0 can be enrolled (up to 20% of overall study population) as long as their allowed csDMARD treatment has been stable for at least 12 weeks prior to Week 0 or if not treated with a csDMARD this regimen is stable for at least 12 weeks prior to Week 0 Visit. In these cases, csDMARD date of first use, dosage, maximum dosage and reason for use as well as

RA disease activity score at time of first dose and all subsequent disease activity assessments (if available) should be documented and must be recorded on the appropriate eCRF. A decrease in the dose of csDMARD due to an event of tolerability or other safety related is allowed during the 12 weeks period prior to the Week 0 Visit and throughout the study as long as well documented.

When no csDMARDs has been used for at least 12 weeks prior to Week 0 Visit, date and reasons for stopping previous csDMARDs must be recorded in the eCRF. The allowed RA concomitant medications should be kept stable throughout the Lead-In and Double-Blind Periods of the study.

Section 5.2.3.2 Concomitant Therapy

Subsection Methotrexate:

Previously read:

All subjects must be treated with MTX and maintain a stable dose (any dose; oral or sc are allowed) from the 12 weeks prior to Screening and throughout the study. In the event of tolerability (or other safety) issues related with MTX, the doses can be decreased and/or resumed as needed during the study.

Has been changed to read:

All subjects who were on MTX at inclusion must maintain a stable dose (any dose; oral, intra-muscular or sc) from the 12 weeks prior to Week 0 Visit and throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues related with MTX, the doses can be decreased and/or resumed as needed during the study and these changes documented.

Section 5.2.3.2 Concomitant Therapy

Subsection Other Disease-Modifying Antirheumatic Drugs (DMARDs),

Corticosteroids or Other Medications for RA:

First, second, third, fourth and fifth paragraph previously read:

Allowed concomitant csDMARDs (chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and

leflunomide) must be a stable dose for at least 12 weeks prior to Screening and at a stable dose throughout the study in the randomized double-blind arms.

Concomitant use of oral corticosteroids (< 10 mg/day oral prednisone or equivalent) is allowed during the study and should be kept at a stable dose from 4 weeks prior to Screening and throughout the study in the randomized double-blind arms.

Concomitant use of oral NSAIDs is allowed during the study and should be kept at a stable dose from 4 weeks prior to Screening and throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues, the doses of NSAIDs may be skipped, decreased and/or resumed as many times as needed during the study. On the days that subjects are scheduled to be seen in clinic, no regularly scheduled NSAIDs should be used within 12 hours of the subject's clinic visit.

Doses of all the RA treatment concomitant medications must remain stable throughout study participation (except as medically required due to an AE and in the rescue therapy arm; Section 5.3.4.1.2).

Folic acid supplementation during the study treatment period: All subjects should take a dietary supplement of oral folic acid 5 mg once weekly throughout the treatment period. Folate should not be administered on the day that MTX study medication is taken, nor on the following day.

Has been changed to read:

Allowed other concomitant csDMARDs (chloroquine, hydroxychloroquine, sulfasalazine, gold formulations [including auranofin, gold sodium thiomalate, and aurothioglucose] and leflunomide) must be at a stable dose for at least 12 weeks prior to Week 0 Visit and at a stable dose throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues related with the csDMARDs, the doses can be decreased and/or resumed as needed during the study and these changes documented.

Concomitant use of oral corticosteroids (< 10 mg/day oral prednisone or equivalent) is allowed during the study and should be kept at a stable dose from 4 weeks prior to Week 0 Visit and throughout the study in the randomized double-blind arms.

Concomitant use of oral NSAIDs, tramadol or other equivalent opioids and non-opioid analgesics is allowed during the study and should be kept at a stable dose and/or therapeutic scheme from 4 weeks prior to Week 0 Visit and throughout the study in the randomized double-blind arms. In the event of tolerability (or other safety) issues, the doses of NSAIDs may be skipped, decreased and/or resumed as many times as needed during the study. On the days that subjects are scheduled to be seen in clinic, no regularly scheduled NSAIDs should be used within 12 hours of the subject's clinic visit.

Doses of all the RA treatment concomitant medications must remain stable throughout study participation (except as medically required due to an AE and in the rescue therapy arm; Section 5.3.4.1.2).

Folic acid supplementation during the study treatment period: All subjects treated with concomitant MTX should take a dietary supplement of oral folic acid 5 mg once weekly or per local guidelines per the investigator's discretion throughout the treatment period. Folate should not be administered on the day that MTX study medication is taken, nor on the following day.

Section 5.2.3.3 Prohibited Therapy

Sixth bullet previously read:

Opioid analgesics (other than tramadol) or marijuana.

Has been changed to read:

Opioid analgesics (other than tramadol or other equivalent opioid analgesics) or marijuana.

Section 5.2.3.4 Rescue Therapy

Third and fourth bullet previously read:

- Corticosteroids (in a dose up to > 15 mg prednisolone or equivalent/day and up to a maximum of 3 injections i.a. during the 16 weeks)
- csDMARDs and/or the dose of MTX

Has been changed to read:

- Corticosteroids (in a dose up to a maximum of 15 mg oral prednisolone or equivalent/day and up to 3 injections i.a. within the follow-up period of 16 weeks)
- csDMARDs including MTX (initiation and/or dose or administration mode change) and excluding not allowed csDMARDs (e.g., azathioprine, cyclophosphamide, d-penicilamine)

Section 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

First paragraph previously read:

Subjects will be allowed a visit window of ± 7 days for all study visits (with the exception of the Screening Period, Lead-In Period and the dbBaseline Visit). If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Week 0).

Has been changed to read:

Subjects will be allowed a visit window of ± 7 days for all study visits (with the exception of the Screening Period, Lead-In Period and the dbBaseline Visit). For the lead-in period and the dbBaseline period a visit window of ± 3 days is recommended. For exceptional cases, the Study designated Physician should be consulted. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Week 0) between Weeks 0 and 4 Visits. Once the subject is randomized, all doses should be based on the date of randomization (Week 4).

Table 1. Study Activities
Header row previously read:

Activity	SCR ^a (21 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare				Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0				ET	UV	70-Day F/U Visit/ Call
			Week				Flare Week						
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p			

Has been changed to read:

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare				Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0				ET ^d	UV	70-Day F/U Visit/ Call
			Week				Flare Week						
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p			

**Table 1. Study Activities
Activity "DAS28 (ESR)" previously read:**

Activity	SCR ^a (21 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare					Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0				70-Day F/U Visit/ Call			
			Week					Flare Week							
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4		10	16	ET
DAS28 (ESR)	X	X ^d	X	X	X	X	X	X	X	X	X	X	X	X	X

Has been changed to read:

Activity	SCR ^a (28 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare					Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0				70-Day F/U Visit/ Call			
			Week					Flare Week							
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4		10	16	ET ^d
DAS28 (ESR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Activities
Delete: Activity "Clinical Disease Activity Index (CDAI)/Simplified Disease Activity Index (SDAI)"

Activity	SCR ^a (21 Days)	Lead-In Period (Week 0)	Randomized Double-Blind Period ESR should be evaluated prior to other study procedures to assess DAS28 and check for flare							Open-Label Rescue Arm When subject has confirmed flare, any visit after Double-Blind Baseline becomes Flare Week 0				70-Day F/U Visit/ Call		
			Week							Flare Week						
			dbBaseline (Week 4)	10	16	22	28	34	40	0 ^p	4	10	16		ET	UV
Clinical Disease Activity Index (CDAI)/Simplified Disease Activity Index (SDAI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Table 1. Study Activities

Table note "d." and "l." previously read:

- d. The ESR from Screening should be used to calculate the DAS28 (ESR) assessment at Day 1.
- l. All females of childbearing potential will have a urine sample collected at dbBaseline prior to study enrollment and at study discontinuation/completion. The samples will be sent to the central laboratory for urine pregnancy testing. Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study.

Has been changed to read:

- d. For those subjects who have entered the study at Week 0 but are early terminated before the Week 4 visit, a short Early Termination visit is allowed. This visit would include reason for discontinuation, review of adverse events, and investigational product/diary return. This will be followed by a 70-day follow-up call/visit. Additional assessments are allowed per the Investigator's discretion.
- l. All females of childbearing potential will have a urine sample collected at the Week 0 visit prior to study enrollment and at study discontinuation/completion. The samples will be tested locally by designated study personnel. Monthly pregnancy tests will be performed throughout the study if required by country regulatory authorities. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to enrollment or continuation in the study. Investigators may conduct more frequent urine pregnancy testing as necessary according to their judgment.

Table 1. Study Activities

Table note "g."

Add: new last sentence

A CXR may be required for evaluation of active TB.

Section 5.3.1.1 Study Procedures

Subsection Inclusion/Exclusion Criteria

Last paragraph previously read:

At the dbBaseline Visit (Week 4), in order for the subject to be randomized, another DAS28 (ESR) must be completed and fulfill the requirement of < 2.6. The ESR from the dbBaseline Visit must be used for this assessment.

Has been changed to read:

At the dbBaseline Visit (Week 4), in order for the subject to be randomized, another 4 variables DAS28 (ESR) must be completed and fulfill the requirement of < 2.6. The

ESR from the dbBaseline Visit must be used for this assessment. If the subject does not meet the DAS28 (ESR) requirement of < 2.6 at the dbBaseline (Week 4), the subject must be discontinued from the trial.

Section 5.3.1.1 Study Procedures
Subsection DAS28 (CRP) and DAS28 (ESR)
Previously read:

The DAS28 (ESR)^{29,63} will be completed at all designated study visits listed in Table 1. The DAS28 (ESR) should be calculated using all parameters including ESR from the current visit.

The DAS28 (ESR) calculation used for study eligibility, enrollment and monitoring will be calculated by the eCRF as below:

$$\text{DAS28(4)} = 0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \text{natural logarithm} \\ (\ln)(\text{ESR}^{\#}) + 0.014 \times \text{Global Health (GH)}^{\gg}$$

- * TJC28 refers to the Subject's total Tender Joint Count out of the provided 28 evaluated joints.
- ** SJC28 refers to the Subject's total Swollen Joint Count out of the provided 28 evaluated joints.
- # ESR refers to Erythrocyte Sedimentation Rate evaluated at the site at current visit and expressed in mm/hg (1st hour).
- » GH refers to the Subject's Global Assessment of Disease Activity (PGA).

DAS28 (CRP)²⁹ maybe calculated based on patient chart review for study Screening as below:

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

- * TJC28 refers to the Subject's total Tender Joint Count out of the provided 28 evaluated joints.
- ** SJC28 refers to the Subject's total Swollen Joint Count out of the provided 28 evaluated joints.
- & CRP refers to the c-reactive protein lab value. CRP unit in the DAS28 (CRP) equation is expressed as mg/L.
- » GH refers to the Subject's Global Assessment of Disease Activity (PGA).

Has been changed to read:

The 4 variables DAS28 (ESR)^{29,72} will be completed at all designated study visits listed in [Table 1](#). The DAS28 (ESR) should be calculated using all parameters including ESR from the current visit.

The 4 variables DAS28 (ESR) calculation used for study eligibility, enrollment and monitoring will be calculated by the eCRF as below. Upon discussion with the SDP, the 3 variable DAS28 (ESR) can be used during the trial to evaluate flare if the PGA score is not available. For the purpose of chart review for study eligibility and inclusion, the 3 variable DAS28 (ESR) can be used when the Subject's Global Assessment of Disease Activity (PGA) is not available.

4 variables DAS28 (ESR):

$$\text{DAS28-ESR}(4) = 0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \text{natural logarithm} \\ (\ln)(\text{ESR}^{\#}) + 0.014 \times \text{Global Health (GH)}^{\gg}$$

3 variables DAS28 (ESR):

$$\text{DAS28-ESR}(3) = [0.56 \times \sqrt{(\text{TJC28}^*)} + 0.28 \times \sqrt{(\text{SJC28}^{**})} + 0.70 \times \ln(\text{ESR}^{\#})] \times 1.08 + \\ 0.16$$

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

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

ESR refers to Erythrocyte Sedimentation Rate evaluated at the site at current visit and expressed in mm/hr (1st hour).

» GH refers to the Subject's Global Assessment of Disease Activity (PGA).

DAS28 (CRP)²⁹ maybe calculated based on patient chart review for study Screening as below:

4 variables DAS28 (CRP):

4 or 3 (if PGA is not available) variables $DAS28-CRP (4) = 0.56 \times \sqrt{(TJC28^*)} + 0.28 \times \sqrt{(SJC28^{**})} + 0.36 \times \ln(CRP^{\&+1}) + 0.014 \times GH^{\gg} + 0.96$

3 variables DAS28 (CRP):

$DAS28-CRP (3) = [0.56 \times \sqrt{(TJC28^*)} + 0.28 \times \sqrt{(SJC28^{**})} + 0.36 \times \ln(CRP^{\&+1})] \times 1.10 + 1.15$

- * TJC28 refers to the Subject's total Tender Joint Count out of the provided 28 evaluated joints.
- ** SJC28 refers to the Subject's total Swollen Joint Count out of the provided 28 evaluated joints.
- & CRP refers to the c-reactive protein lab value. CRP unit in the DAS28 (CRP) equation is expressed as mg/L.
- » GH refers to the Subject's Global Assessment of Disease Activity (PGA).

Section 5.3.1.1 Study Procedures

Subsection Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)

First paragraph previously read:

CDAI⁶⁴ and SDAI^{64,65} will be completed at visits according to the scheduled in Table 1. The SDAI should be calculated using all parameters including CRP from the same visit (and so calculated at next Visit).

Has been changed to read:

CDAI⁷³ and SDAI^{73,74} will be completed at visits according to the scheduled in Table 1. The SDAI and CDAI will be calculated as part of the statistical analysis using all parameters including CRP from the same visit (and as such calculated at the next Visit).

Section 5.3.1.1 Study Procedures

Subsection Musculoskeletal Ultrasound (US)

First paragraph, last sentence previously read:

If they decide to and the pre-requirements criteria are met (as per the Ultrasound manual), they should perform US for every subject they recruit at time points indicated by the protocol.

Has been changed to read:

If they decide to and the pre-requirements criteria are met (as per the Ultrasound manual), they should perform US for every subject they recruit at time points indicated by the protocol; exceptions are allowed upon discussion with Study Designated Physician. For sites participating in the ultrasound assessments, all subjects from the site should undergo the US scans and assessments as per protocol;

Section 5.3.1.1 Study Procedures
Subsection Musculoskeletal Ultrasound (US)
Second paragraph, fifth sentence previously read:

The assessments and scoring will be locally performed.

Has been changed to read:

The assessments and scoring will be locally performed and afterwards the report of US assessments from all subjects will be sent to the central Imaging vendor. For the first subject enrolled and for the first subject with flare assessments further procedures for quality assessment are required (as per ultrasound manual).

Section 5.3.1.1 Study Procedures
Subsection Musculoskeletal Ultrasound (US)
Third paragraph previously read:

The optional US will be performed during the Lead-In Period or at the dbBaseline Visit prior to randomization and at Flare Week 0 Visit (when applicable) to assess synovial hypertrophy, tenosynovitis and erosions through gray scale ultrasonography (GSUS) and synovitis/vascularization through Power Doppler Ultrasonography (PDUS).

Has been changed to read:

The optional US will be performed during the Lead-In Period or at the dbBaseline Visit prior to randomization and at Flare Week 0 Visit (when applicable and at or up to 7 days after the visit) to assess synovial hypertrophy, tenosynovitis and erosions through gray

scale ultrasonography (GSUS) and synovitis/vascularization through Power Doppler Ultrasonography (PDUS).

Section 5.3.1.1 Study Procedures

Subsection Magnetic Resonance Imaging (MRI)

First paragraph previously read:

An MRI of the most affected or of the dominant hand (2nd to 5th MCP) and wrist (if both sides are considered equally affected) will be performed to all subjects during the Screening/Lead-In Period (prior to dbBaseline Visit) and the Final/Early Termination Visit (if last MRI \geq 12 weeks before).

Has been changed to read:

An MRI of the most affected or of the dominant hand (2nd to 5th MCP) and wrist (if both sides are considered equally affected) will be performed to all subjects during the Lead-In Period (prior to dbBaseline Visit) and the Final/Early Termination Visit (if last MRI \geq 12 weeks before).

Section 5.3.1.1 Study Procedures

Subsection TB Screening

First paragraph previously read:

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or a Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed locally during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration. If a subject had a negative PPD or IGRA test within 12 months prior to Screening, and all protocol required documentation is available, this test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases must be discussed with the AbbVie Study Designated Physician.

Has been changed to read:

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or a Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) must be performed during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

Subjects that have a negative PPD or IGRA test and are considered at risk for having latent TB (any immunosuppressed patient with a strong suspicion of TB exposure and no prior vaccination with Bacille Calmette-Guérin) need to be evaluated by a TB expert before Week 0.

Subjects at risk for TB exposure are defined as:

- subjects that have household contact with a person with active TB
- subjects living in areas with high incidence of TB
- subjects that frequently visits areas with high prevalence of active TB

If a subject had a negative PPD or IGRA test within 12 months prior to Screening, and all protocol required documentation is available, this test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases must be discussed with the AbbVie Study Designated Physician.

Section 5.3.1.1 Study Procedures

Subsection TB Screening

Seventh paragraph previously read:

If the PPD or the IGRA test is positive or the subject has a CXR indicative of latent TB, the subject will be required to initiate and have taken at least 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of the United States Center for Disease Control (CDC) recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy.

Has been changed to read:

If the PPD or the IGRA test is positive or the subject has a CXR or TB expert opinion indicative of latent TB, the subject will be required to initiate and have taken at least 2 weeks (or per local guidelines, whichever is longer) of an ongoing course of the United States Center for Disease Control (CDC) and Prevention recommended prophylaxis or prophylaxis per local guidelines prior to starting study therapy.

Section 5.3.1.1 Study Procedures

Subsection TB Screening

Eighth paragraph

Add: new last sentence

The prophylactic treatment must be maintained during the study until its recommended full course is completed.

Section 5.3.1.1 Study Procedures

Subsection TB Screening

Delete: last paragraph and bullet list

For sites participating in the Czech Republic, the following local requirements will also be applicable:

- A pulmonologist will be responsible to obtain a detailed medical history with respect to TB exposure. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or reside or work in TB endemic locations. The information obtained by the pulmonologist must be documented in the subject's source note, dated and signed by the pulmonologist.
- A pulmonologist must review the results of the PPD skin test or the IGRA test and the chest x-ray and has to give his/her opinion about the eligibility of each subject to be enrolled to the study. This opinion must be documented in writing in the subject's source documents.
- All subjects with a positive PPD or IGRA test need to be approved for entry into the trial by both the Czech pulmonologist and the AbbVie Study Designated Physician and all such subjects need to receive prophylaxis for

latent TB. Under no circumstances can a subject with a positive PPD or IGRA test result and no prior history of treatment for active or latent TB be allowed into this trial.

Section 5.3.1.1 Study Procedures

Subsection Hepatitis B Testing

First paragraph previously read:

If a subject had a negative hepatitis B virus (HBV) result within 12 months prior to Screening and all protocol required documentation is available, these tests repetition are not required.

Has been changed to read:

If a subject had a negative hepatitis B virus (HBV) result within 12 months prior to Screening and all protocol required documentation is available, these tests repetition are not required. At screening subjects must be assessed for high risk of exposure to hepatitis B since their last test. If high risk is suspected, a hepatitis B test should be performed.

Section 5.3.1.1 Study Procedures

Subsection Pregnancy Tests

First paragraph previously read:

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. At the dbBaseline Visit, subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Has been changed to read:

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. At the Week 0 Visit, subjects of childbearing potential will have a

urine pregnancy test performed locally by designated study personnel. Investigators may conduct more frequent urine pregnancy testing as necessary according to their judgment. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory. A lactating or pregnant female will not be eligible for participation or continuation in this study.

Section 5.3.1.1 Study Procedures

Subsection Adverse Events

Second, third and fourth sentence previously read:

Subjects in the Rescue Arm (adalimumab 40 mg sc eow) who continue on adalimumab therapy eow after the end of study participation will not be contacted for follow-up as any new adverse events should be reported through the mechanism used for all postmarketing adverse experiences. All other subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing adverse events. In addition, serious adverse events (SAEs) and protocol-related nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

Has been changed to read:

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination/Final Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events.

Section 5.3.1.1 Study Procedures

Subsection Dispense Study Drug

Add: new second paragraph

Once the limit of 20% of enrolled subjects on other csDMARDs or no csDMARDs is met, only subjects on concomitant methotrexate will be allowed into the trial.

Section 5.4.1 Discontinuation of Individual Subjects

Third paragraph

Add: new second sentence

If subjects discontinue the study during the lead-in observational period, prior to randomization, a short Early Termination visit is required for: returning study material and drug, assess any safety/adverse events, collect reason for discontinuation and a 70-day follow-up call/visit; the remainder of full Early Termination Visit study procedures can be completed per the investigator's discretion.

Section 5.4.1 Discontinuation of Individual Subjects

Fourth paragraph previously read:

A final phone call will be made to the subject approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Has been changed to read:

A final phone call will be made to all subjects approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Section 5.5.1 Treatments Administered

Last paragraph previously read:

Subjects who meet flare criteria will be entering an Open-Label Rescue Arm and OL adalimumab 40 mg will be administered every other week until Week 56 of the trial.

Has been changed to read:

Subjects who meet flare criteria will be entering an Open-Label Rescue Arm and OL adalimumab 40 mg will be administered every other week for 16 weeks.

Section 5.5.5.1 Blinding of Investigational Product
Second paragraph, first sentence previously read:

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie Study Designated Physician (Section 7.0) prior to breaking the blind.

Has been changed to read:

In the event of a medical emergency in which the Investigator believes that knowledge of study drug treatment is required, every effort must be made to contact the AbbVie Study Designated Physician (Section 7.0) prior to breaking the blind as long as it does not compromise subject safety.

Section 5.6.1 Discussion of Study Design and Choice of Control Groups
First sentence previously read:

This Phase 4 study is designed to investigate the association between residual disease activity at baseline, and the occurrence of flares in RA patients on adalimumab in combination with methotrexate in sustained clinical remission (DAS28 [ESR] < 2.6) and submitted to an adalimumab dose tapering regimen or withdrawal.

Has been changed to read:

This Phase 4 study is designed to investigate the association between residual disease activity at baseline, and the occurrence of flares in RA patients on adalimumab who are in sustained clinical remission (DAS28 [ESR] < 2.6) and submitted to an adalimumab dose tapering regimen or withdrawal.

Section 5.6.3 Suitability of Subject Population
First sentence previously read:

Subjects age \geq 18 years diagnosed with RA, on a stable dose of adalimumab 40 mg sc eow (for \geq 12 months prior to Screening Visit) in combination with methotrexate (MTX; at stable dose for \geq 12 weeks prior to the Screening Visit.) and in documented clinical

remission (DAS28 [ESR] 2.6 or DAS28 [CRP]) for ≥ 6 months prior to the study are eligible for this study.

Has been changed to read:

Subjects age ≥ 18 years diagnosed with RA, on a stable dose of adalimumab 40 mg sc qw (for ≥ 12 months prior to Screening Visit) in combination with methotrexate (MTX; at stable dose for ≥ 12 weeks prior to the Screening Visit) or if not on MTX in a stable other allowed csDMARD or no csDMARD regimen for ≥ 12 weeks prior to Week 0 Visit) and in documented clinical remission (DAS28 [ESR] < 2.6 or DAS28 [CRP] 2.6) for ≥ 6 months prior to the study are eligible for this study. Patients who are not on stable concomitant MTX will be allowed as per current clinical practice, but limited to 20% of the study population.

Section 6.0 Complaints

Add: new section number and text

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.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.1.5). For adverse events, please refer to Sections 6.1 through 6.1.7. For product complaints, please refer to Section 6.2.

Section 6.0 through 6.7

Section number and title previously read:

- 6.0 Adverse Events**
- 6.1 Definitions**
- 6.1.1 Adverse Event**
- 6.1.2 Serious Adverse Events**
- 6.2 Adverse Event Severity**
- 6.3 Relationship to Study Drug**
- 6.4 Adverse Event Collection Period**
- 6.5 Adverse Event Reporting**
- 6.6 Pregnancy**
- 6.7 Toxicity Management**

Has been changed to read:

- 6.0 Complaints**
- 6.1 Medical Complaints**
- 6.1.1 Definitions**
- 6.1.1.1 Adverse Event**
- 6.1.1.2 Serious Adverse Events**
- 6.1.2 Adverse Event Severity**
- 6.1.3 Relationship to Study Drug**
- 6.1.4 Adverse Event Collection Period**
- 6.1.5 Adverse Event Reporting**

6.1.6 Pregnancy

6.1.7 Toxicity Management

Section 6.4 Adverse Event Collection Period

Last paragraph previously read:

Subjects in the Rescue Arm (adalimumab 40 mg sc eow) who continue on adalimumab therapy eow after the end of study participation will not be contacted for follow-up as any new adverse events should be reported through the mechanism used for all postmarketing adverse experiences. All other subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs. 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. All SAEs and all ongoing adverse events reported during the 70-day follow-up phone call must be captured in the clinical database.

Has been changed to read:

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects that end study participation early will have an Early Termination/Final Visit. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events. 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.

Section 6.5 Adverse Event Reporting

"Immunology Safety Team" building number previously read:

██████

Has been changed to read:

██████

Section 6.5 Adverse Event Reporting

Add: new fifth paragraph

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: 

Section 6.2 Product Complaint

Add: new section and text, renumber subsequent sections

6.2 Product Complaint

6.2.1 Definition

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

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, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

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

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device 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 (syringe). 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.

Section 7.0 Protocol Deviations
"Alternate Contact:" previously read:

Alternate Contact:



Has been changed to read:

Alternate Contact:



**Section 8.1.4.1 Analysis for Primary Objective
First paragraph, last sentence previously read:**

The 80% and 95% confidence intervals of the odds ratio will also be provided as an addition.

Has been changed to read:

The 95% confidence intervals of the odds ratio will also be provided as an addition.

**Section 8.1.4.1 Analysis for Primary Objective
Second paragraph, last sentence previously read:**

All model based analyses may adjust for dbBaseline clinical patient characteristics including age, disease duration, previous treatment, etc., when appropriate.

Has been changed to read:

All model based analyses may adjust for dbBaseline clinical patient characteristics including age, disease duration, previous and concomitant treatment (such as use of MTX, use of csDMARD as versus TNFi monotherapy), etc., when appropriate.

Section 8.1.4.3 Analysis for Exploratory Objectives

Add: new last paragraph

The occurrence and time to flare from dbBaseline in the concomitant MTX, other csDMARDs and no csDMARDs patients will be analyzed for potential differential effect.

Section 8.1.7 Interim Analysis for Double-Blind Baseline Characteristics

First sentence previously read:

There are few data describing patient disease characteristics including markers of residual inflammation such as sensitive imaging assessments and potential biomarkers as well as drug levels in RA patients who are in sustained clinical remission on a stable treatment with a TNFi and MTX.

Has been changed to read:

There are few data describing patient disease characteristics including markers of residual inflammation such as sensitive imaging assessments and potential biomarkers as well as drug levels in RA patients who are in sustained clinical remission on a stable treatment with a TNFi and MTX and/or with other csDMARDs(s) or in TNFi monotherapy.

Section 8.2 Determination of Sample Size

Previously read:

The planned total number of subjects enrolled into the Lead-In Period is approximately 334.

To estimate the odds ratio for the occurrence of flare with dbBaseline MRI score based on historical MRI and literature^{40,75} data, an effective sample size of 250 subjects in the dose tapering group will ensure a precision for the estimation with the width of 90% CI no

more than 0.1 for an odds ratio 1.2, no more than 0.4 for an odds ratio 1.5, and no more than 1.0 for an odds ratio 1.8. Such sample size will also ensure a precision for the estimation of a continuous correlation coefficient ρ with the half width of 90% CI of ρ no more than 0.1 for a mild correlation coefficient 0.2, no more than 0.09 for a moderate correlation coefficient 0.4, and no more than 0.07 for a higher correlation with $\rho = 0.6$. Assuming a 30% flare rate^{20-22,24}, this sample size will provide the precision that the 2-sided 90% CI of the flare rate has a half width no more than 5%.

Under a 5:1 randomization ratio (dose tapering versus withdrawal), a total of 300 subjects will be randomized. Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 334 subjects will need to be enrolled into the Lead-In Period.

Has been changed to read:

The planned total number of subjects enrolled into the Lead-In Period is approximately 200.

A recently published study (DOSERA) showed that 56% (15/27 patients) of patients who were previously in low disease activity had treatment failure within 48 weeks after reducing the dose of etanercept; the median time to failure was 36 weeks (95% CI:15.6-NE).⁸⁹ The STRASS study, also published in 2015, showed in a similar RA patient population, that progressive tapering of TNFi therapy (adalimumab or etanercept) was associated with flare in 76.6% (49/64) of patients throughout the study duration; importantly, 28.8% of patients flared after the first step of tapering (adalimumab 40 mg q3 weeks or etanercept 50 mg q10 days) and the median time to flare was 9 months.⁹⁰ In another tapering study (DRESS) a cumulative incidence of short-lived flares in a progressive tapering of TNFi of 55% at 9 months (and 73% at 18 months) was observed. Among these studies, the DRESS study had the higher sample size with 121 patients in the taper arm but only 43% successfully tapered the TNFi. None of these studies was designed or powered to evaluate predictors of flare neither found definite predictors upon further statistical analysis. A proof of concept study conducted in 44 RA patients in clinical remission receiving treatment with a bDMARD has shown that residual synovial

inflammation determined by comprehensive ultrasound assessment predicted relapse within a short term after discontinuation of the treatment.⁹¹

These data provided the rationale for assuming a conservative flare rate of 30% and for our sample size calculation.

To estimate the odds ratio for the occurrence of flare with baseline MRI score based on historical MRI data, an effective sample size of 150 subjects in the dose tapering group will ensure a precision for the estimation with the width of 90% CI no more than 0.03 for an odds ratio 1.03, no more than 0.07 for an odds ratio 1.1, and no more than 0.14 for an odds ratio 1.2. Such sample size will also ensure a precision for the estimation of a correlation coefficient ρ with the width of 90% CI of ρ no more than 0.26 for a mild correlation coefficient 0.28, no more than 0.18 for a moderate correlation coefficient 0.55, and no more than 0.13 for a higher correlation with $\rho = 0.67$. Assuming a 30% flare rate, this sample size will provide the precision that the 2-sided 90% CI of the flare rate has a half width no more than 6%.

Sensitivity precision levels under various assumptions are presented in [Table 4](#).

Under a 5:1 randomization ratio (dose tapering versus withdrawal), a total of 180 subjects will be randomized. Accounting for a 10% discontinuation rate during the Lead-In Period, approximately 200 subjects will need to be enrolled into the Lead-In Period.

Table 4. Sample Size Assumptions

True Odds Ratio	Flare Rate	Sample Size (Dose Tapering Arm)	OR from Logistics Regression (90% CI) : CI Width	Correlation (90% CI) : CI Width
1.03	30%	150	1.03 (1.02, 1.05) : 0.03	0.28 (0.14, 0.40) : 0.26
1.1	30%	150	1.1 (1.07, 1.14) : 0.07	0.55 (0.46, 0.64) : 0.18
1.2	30%	150	1.21 (1.15, 1.29) : 0.14	0.67 (0.61, 0.73) : 0.13

Section 10.3 Electronic Patient Reported Outcomes (ePROs)

Add: new section title and text

10.3 Electronic Patient Reported Outcomes (ePROs)

An electronic patient-recorded outcomes (ePRO) device will be provided to subjects during screening and will be completed at all subject visits in the office. An additional device will be given to subjects at their flare Week 0 visit (if applicable) and will be completed at home weekly. Site personnel will provide training on the proper use of the e-Diary. These data will be uploaded to a server, the data on the server will be considered source, and maintained and managed by CRF Health. Patient reported data are completed for each subject screened/enrolled in this study. An ePRO tool called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA, will be used to collect this data. The ePRO system is in compliance with Title 21 CFR Part 11.

Internet access to the ePRO data will be provided by CRF Health for the duration of the trial. This access will be available for the duration of the trial to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO 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 print-outs from that media.

The electronic device may be programmed to allow data entry for only certain periods of time. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The investigational site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Section 15.0 Reference List

Add: new Reference 33 – 40

33. Madsen OR. Agreement between DAS-CRP with 3 and 4 variables in patients with rheumatoid arthritis treated with biological agents in the daily clinic. *J Rheumatol.* 2013;40(4):379-85.
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36. Soliman MM, Ashcroft, DM, Watson KD, et al. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis.* 2011;70(4):583–9.
37. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low-- results from RABBIT, the German biologics register. *Arthritis Res Ther.* 2006;8(3):R66. Epub 2006 Apr 5.
38. Heiberg MS, Koldingsnes W, Mikkelsen K, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis Rheum.* 2008;59(2):234–40.
39. Askling J, Fored CM, Brandt L, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. *Ann Rheum Dis.* 2007;66(10):1339–44.

40. Manders S, Kievit W, Jansen T, et al. Significantly better results for TNFI combination therapy with MTX than TNFI mono- and combination without MTX therapy in patients with RA: results from the dream registry. *Ann Rheum Dis*. 2013;72:A73-4.

Section 15.0 Reference List

Add: new Reference 89 – 91

89. van Vollenhoven RF, van der Maas A, Minten MJ, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. *BMJ*. 2015;9;350:h1389. doi: 10.1136/bmj.h1389.
90. Fautrel B, Pham T, Alfaiate T, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid Arthritis Study). *Ann Rheum Dis*. 2016;75(1):59-67.
91. Iwamoto T, Ikeda K, Hosokawa J, et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission: high predictive values of total gray-scale and power Doppler scores that represent residual synovial inflammation before discontinuation. *Arthritis Care Res (Hoboken)*. 2014;66(10):1576-81.

Section 15.0 Reference List

Delete: Reference 75

- Peterfy C, Durez P, Haraoui B, et al. Responses to early rheumatoid arthritis (RA) to treatment with adalimumab plus methotrexate vs. Methotrexate alone: magnetic resonance imaging results from OPTIMA. *Ann Rheum Dis*. 2010;69 Suppl 3:455.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[Redacted]		Medical Affairs
		Statistics
		Pharmacokinetics
		Medical Affairs
		Clinical

Has been changed to read:

Name	Title	Functional Area
[Redacted]		Global Medical Affairs
		Statistics
		Global Medical Affairs
		Clinical
		Pharmacokinetics
		Bioanalytics
		Regulatory Affairs
[Redacted]		Clinical

Appendix C. Injection Instructions – Pre-Filled Syringe – Sample
Subsection Study Drug Dosing Schedule

Fourth paragraph, second and third bullet previously read:

- At Week 4 at the start of the Double-Blind Period, you will receive 3 syringes. At the Week 4 Visit, you will administer the injection at the clinic. You will take the other 2 home to be administered at Week 7 and Week 10. During the remainder of the Double-Blind Period (Weeks 10, 16, 22, 28 and 34), you will receive 2 syringes at each visit to be taken at Weeks 13, 16, 19, 22, 25, 28, 31, 34 and 37, respectively.
- If at any time you have a flare and it is confirmed, you will enter the Open-Label Rescue Arm and start a Flare Week 0 Visit. You will administer an injection of open-label adalimumab at the clinic. *You must return all double-blind medication at the next visit.*

- At the Flare Week 0 Visit, you will also receive 2 additional syringes to administer at Flare Weeks 2 and 4.
- At the Flare Week 4 Visit, you will receive 3 syringes to be taken at Flare Weeks 6, 8 and 10.
- At the Flare Week 10 Visit, you will receive 2 additional syringes to be taken at Weeks 12 and 14.
- If your time of injection falls on a clinic day, you must inject study drug after all study procedures are performed (not prior).

Has been changed to read:

- At Week 4 at the start of the Double-Blind Period, you will receive 2 syringes. At the Week 4 Visit, you will administer the injection at the clinic. You will take the other 1 syringe home to be administered at Week 7. During the remainder of the Double-Blind Period (Weeks 10, 16, 22, 28 and 34), you will receive 2 syringes at each visit to be taken (one to be administered at the visit and the other to be taken at home 3 weeks later) at Weeks 10, 13, 16, 19, 22, 25, 28, 31, 34 and 37, respectively.
- If at any time you have a flare and it is confirmed, you will enter the Open Label Rescue Arm and start a Flare Week 0 Visit. *You must return all double-blind medication at the next visit.*
 - At the Flare Week 0 Visit, you will receive 2 syringes. One injection of open-label adalimumab will be administered at the clinic. You will take the other 1 syringe home to be administered 2 weeks later at Flare Week 2.
 - At the Flare Week 4 and 10 Visits, you will receive 3 syringes at each visit (one to be administered at the visit and the other 2 to be taken separately at home every two weeks) to be taken at Flare Weeks 4, 6, 8, 10, 12, 14 respectively.
 - If your time of injection falls on a clinic day, you must inject study drug after all study procedures are performed (not prior).

**Appendix K Short Form-36 (SF-36) Health Survey Questionnaire – Sample
Previously read:**

<h2>Your Health and Well-Being</h2>

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅

3. The following questions are about activities you might do during a typical day.
Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
--	--	-------------------------------	----------------------------------	-----------------------------------

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
--	-------------------------	--------------------------	-----------------------------	---------------------------------	--------------------------

^a Cut down on the amount of time you spent on work or other activities

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^b Accomplished less than you would like

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^c Were limited in the kind of work or other activities

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

^d Had difficulty performing the work or other activities (for example, it took extra effort)

<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
----------------------------	----------------------------	----------------------------	----------------------------	----------------------------

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
^a Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^b <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^c Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
^a Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^b Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^d Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^e Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^f Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^g Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^h Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
ⁱ Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How **TRUE** or **FALSE** is **each** of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
^a I seem to get sick a little easier than other people	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^b I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^c I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
^d My health is excellent	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

THANK YOU FOR COMPLETING THESE QUESTIONS

Has been changed to read:

Your Health and Well-Being

SF-36v2[®] Health Survey[©] 1992, 1996, 2000, 2010
Medical Outcomes Trust and
QualityMetric Incorporated.

All Rights Reserved.

SF-36[®] is a registered trademark of
Medical Outcomes Trust.
(SF-36v2[®] Health Survey Standard,
United States (English))

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one box that best describes your answer.

In general, would you say your health is:

Excellent
Very good
Good
Fair
Poor

Compared to one year ago, how would you rate your health in general now?

- Much better now than one year ago
- Somewhat better now than one year ago
- About the same as one year ago
- Somewhat worse now than one year ago
- Much worse now than one year ago

The following question is about activities you might do during a typical day.

Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in lifting or carrying groceries? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in climbing several flights of stairs? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in climbing one flight of stairs? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in bending, kneeling, or stooping? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in walking more than a mile? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in walking several hundred yards? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in walking one hundred yards? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

The following question is about activities you might do during a typical day.

Does your health now limit you in bathing or dressing yourself? If so, how much?

- Yes, limited a lot
- Yes, limited a little
- No, not limited at all

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Cut down on the amount of time you spent on work or other activities as a result of your physical health

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Accomplished less than you would like as a result of your physical health

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Were limited in the kind of work or other activities as a result of your physical health

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities?

Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all
Slightly
Moderately
Quite a bit
Extremely

How much bodily pain have you had during the past 4 weeks?

None
Very mild
Mild
Moderate
Severe
Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all
A little bit
Moderately
Quite a bit
Extremely

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel full of life?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been very nervous?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt calm and peaceful?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you have a lot of energy?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt downhearted and depressed?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel worn out?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been happy?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel tired?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

How TRUE or FALSE is the following statement for you?

I seem to get sick a little easier than other people.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

I am as healthy as anybody I know.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

I expect my health to get worse.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

How TRUE or FALSE is the following statement for you?

My health is excellent.

Definitely true
Mostly true
Don't know
Mostly false
Definitely false

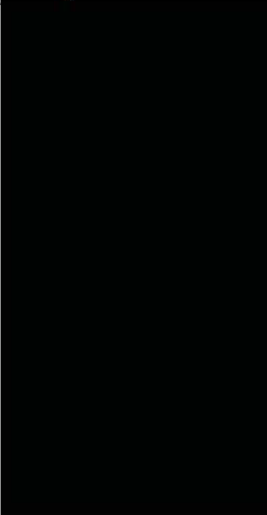
Document Approval

Study M14500 - A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected via Imaging Techniques, Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA) - Amendment 1 - EudraCT 2014-001114-26 - 25Feb2016

Version: 1.0

Date: 26-Feb-2016 04:42:48 PM

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Signed by:	Date:	Meaning Of Signature:
	25-Feb-2016 07:51:52 PM	Author
	25-Feb-2016 07:55:56 PM	Approver
	25-Feb-2016 09:27:04 PM	Approver
	25-Feb-2016 10:43:29 PM	Approver
	25-Feb-2016 11:17:42 PM	Approver
	26-Feb-2016 10:22:31 AM	Approver
	26-Feb-2016 01:45:53 PM	Approver
	26-Feb-2016 04:42:43 PM	Study Director