1.0 Title Page

Clinical Study Protocol M14-496

A Phase 4 open-label randomized controlled study COmparing the effectiveness of adalimumab iNTROduction and methotrexate dose escaLation in subjects with Psoriatic Arthritis (CONTROL)

Incorporating Amendment 1, 2, and 3

AbbVie Investigational Product:	Adalimumab
Date:	03 June 2019
Development Phase:	4
Study Design:	An interventional Phase 4 open-label, randomized, controlled, parallel-group, multi-country study in subjects with psoriatic arthritis (PsA) consisting of 2 parts: Part 1 is designed to compare the achievement of minimal disease activity (MDA) between subjects randomized to either adalimumab in combination with methotrexate (MTX) or MTX alone escalated to the highest recommended or tolerable dose; Part 2 is to evaluate the maintenance or achievement of MDA on four different treatment regimens using adalimumab and/or MTX, with subject allocation based on the initial randomized treatment and achievement of MDA in Part 1, and with rescue treatment option.
EudraCT Number:	EudraCT 2016-000191-21
Investigator:	Investigator information is on file at AbbVie.
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* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	28 April 2016
Amendment 1	10 October 2016
Amendment 2	09 March 2018

The purpose of this amendment is to:

- Update Section 5.5.7, Drug Accountability, to remove requirement for onsite monitor confirmation of empty boxes, bottles and returned Sharps containers.

  Rationale: *Investigative site staff is responsible for drug accountability and destruction per their approved process. Remote monitoring is conducted to ensure information documented is consistent with the investigative site's process.*
- Update Section 8.0, Statistical Methods and Determination of Sample Size.
- To update the pre-specified analysis for the continuous endpoints to be MMRM.

  Rationale: *MMRM was originally planned as a sensitivity analysis for continuous endpoints. Given that MMRM is a more robust statistical method in terms of missing data handling as compared to ANCOVA using LOCF, it's now elevated to be the primary analysis for continuous endpoints.*
- To update the sensitivity analysis for the primary endpoint to be CMH test based on Observed Cases (OC).

  Rationale: *Originally planned sensitivity analysis was logistic regression. This is being changed to a CMH test based on OC because this is a more appropriate sensitivity analysis for the response rate difference which is how the primary analysis is being reported.*
- To remove pre-specified sensitivity analysis for secondary endpoints.

Rationale: *Pre-specified sensitivity analyses are deemed not to be necessary for non-key secondary endpoints. Additional sensitivity analysis for secondary endpoints may be performed post-hoc.*

- To remove pre-specified treatment group homogeneity analysis and p values for demographics and baseline disease characteristics.

  Rationale: *Homogeneity analysis and p values for demographics and baseline disease characteristics are only meaningful with appropriate sample size otherwise a tiny difference which may not be clinically meaningful can have a significant p value. In addition, this is a randomized study, so demographics and baseline characteristics are expected to be similar by the study design. Further testing using p values are not needed. Therefore, descriptive statistics is used to demonstrate the similarity for the demographics and baseline characteristics. Additional analysis on exploring baseline characteristics may be performed post hoc.*

- To remove formal summary of pre- and post-treatment Adverse Event analysis.

  Rationale: *Pre- and post-adverse events will be provided in the AE listing.*

- To update the language in the lab change from baseline analysis.

  Rationale: *Observed values of vital signs and laboratory variables at each visit will be summarized for all treated subjects. In addition, the change from baseline for lab variables of interest will be provided.*

- To update the language in Section 8.2 Determination of sample size.

  Rationale: *For added accuracy.*

- To make editorial changes throughout for clarity
- The following administrative changes were made:
  - Update Section 1.0, Title Page, to update Sponsor/Emergency contact information.
  - Update Section 1.2, Synopsis, to make editorial changes for clarity and to align with updates made in Section 8.0, Statistical Methods and Determination of Sample Size.
  - Update Section 5.5.2.2, Storage and Disposition of Study Drugs, to clarify temperature excursion reporting.

- Update Section 6.1.5, Adverse Event Reporting, to provide contact information for [redacted], MD.
- Update Section 6.0, Complaints, to make editorial changes for clarity.

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-496
Name of Study Drug: Adalimumab	**Phase of Development:** 4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 03 June 2019
Protocol Title: A Phase 4 open-label randomized controlled study **CO**mparing the effectiveness of adalimumab i**NTRO**duction and methotrexate dose esca**L**ation in subjects with Psoriatic Arthritis (CONTROL)	

Objectives:

Primary Objective

The primary objective is to compare the effectiveness based on the achievement of minimal disease activity (MDA) at Week 16 between subjects who had adalimumab introduced and those that had methotrexate (MTX) escalated to the highest recommended dose of 20 – 25 mg every week (ew) or highest tolerable dose up to 25 mg ew after inadequate disease control on the initial MTX therapy.

Secondary Objectives

- To compare the effectiveness at Week 16 between subjects who had adalimumab introduced and those that had MTX escalated to the highest recommended dose of 20 – 25 mg ew or highest tolerable up to 25 mg ew based on the following clinical, functional and quality of life measures:
  - Psoriatic Arthritis Disease Activity Score (PASDAS)
  - Disease Activity in Psoriatic Arthritis (DAPSA) score
  - Psoriatic Arthritis Impact of Disease (PsAID) score
  - American College of Rheumatology criteria (ACR)
  - Disease Activity Score 28 (DAS28)
  - Psoriasis Area and Severity Index (PASI)
  - Health Assessment Questionnaire Disability Index (HAQ-DI)
  - Short Form Health Survey 36 (SF-36) scores: total, physical component summary (PCS) and mental component summary (MCS)
  - Dermatology Life Quality Index (DLQI)
  - Leeds Enthesitis Index (LEI)
  - Tender dactylitic digit count
- To evaluate the achievement of MDA at Week 32 on each of the four different treatment regimens involving adalimumab and/or MTX in Part 2 of the study.

The study also has the following **Exploratory Objectives:**

- To evaluate the effectiveness at Week 32 based on the clinical, physical function and quality of life measures described under the secondary objectives on each of the four different treatment regimens involving adalimumab and/or MTX in the second part of the study.
- To evaluate ultrasound detected synovitis and enthesitis at joint and enthesis level, and treatment effect on each of the study treatment regimens.

Objectives (Continued):

Exploratory Objectives (Continued)

- To assess the pharmacokinetic and immunogenicity of adalimumab with and without concomitant MTX.
- To investigate various biomarkers and their associations with treatment responses and outcomes.

Investigators: Multi-center

Study Sites: Approximately 60 sites

Study Population: Approximately 240 adult subjects with active PsA (defined as not in MDA and having at least 3 tender and 3 swollen joints) despite having been treated with the first course of MTX at the dose of 15 mg ew for ≥ 4 weeks and biologic naive who meet all the inclusion and none of the exclusion criteria are planned to be enrolled in the study.

Number of Subjects to be Enrolled: 240 subjects in total, 120 subjects per randomized arm.

Methodology: This interventional Phase 4 open-label, randomized, controlled, parallel-group, multicenter study will be conducted in two (2) parts, each of 16-week duration.

Part 1 (Day 1-Week 16) is designed to compare the achievement of MDA on adalimumab introduced in combination with MTX versus MTX alone escalated to the highest recommended dose of 20 – 25 mg ew or highest tolerable dose up to 25 mg ew, whatever feasible, in PsA subjects inadequately controlled after the initial course of MTX at 15 mg ew. Part 1 will be open-label, randomized, controlled, parallel group.

Part 2 (Week 16-32) is to evaluate the effectiveness of four (4) different treatment regimens consisting of adalimumab and/or MTX in maintaining or attaining MDA, as applicable. Part 2 will be open-label, parallel group. Subjects will be assigned into the four treatment arms based on their MDA status at Week 16 and initial randomized treatment. Starting at Week 24, there will be rescue treatment option based on not achieving MDA and investigator's judgment.

Following a maximum 30-day screening period, subjects meeting the selection criteria will be randomized in a 1:1 ratio to either of the two (2) arms and treated for 16 weeks in Part 1:

- Arm 1/Part 1: Adalimumab 40 mg eow in combination with MTX 15 mg ew (adalimumab 40 mg eow + MTX 15 mg ew),
- Arm 2/Part 1: MTX escalated to 20 – 25 mg or highest tolerable dose ew (MTX 20 – 25 mg or highest tolerable dose ew)*
  - * MTX will be escalated by increments of 5.0 mg every 2 weeks, starting at 20 mg ew as the first MTX dose on or after Day 1, depending on the subject's MTX administration schedule prior to the study. In the case of suspected MTX intolerance or toxicity, the MTX dose may be de-escalated by 5 mg and the subject may stay on the highest tolerable MTX dose below 20 – 25 mg ew as described per the protocol. MTX dose should not exceed 25 mg ew in this study.

Methodology (Continued):

After the assessment of MDA at Week 16 (primary endpoint), subjects will be assigned to one of the 4 treatment arms based on the achievement of MDA and initial randomized treatment, and treated for additional 16 weeks in Part 2 as follows:

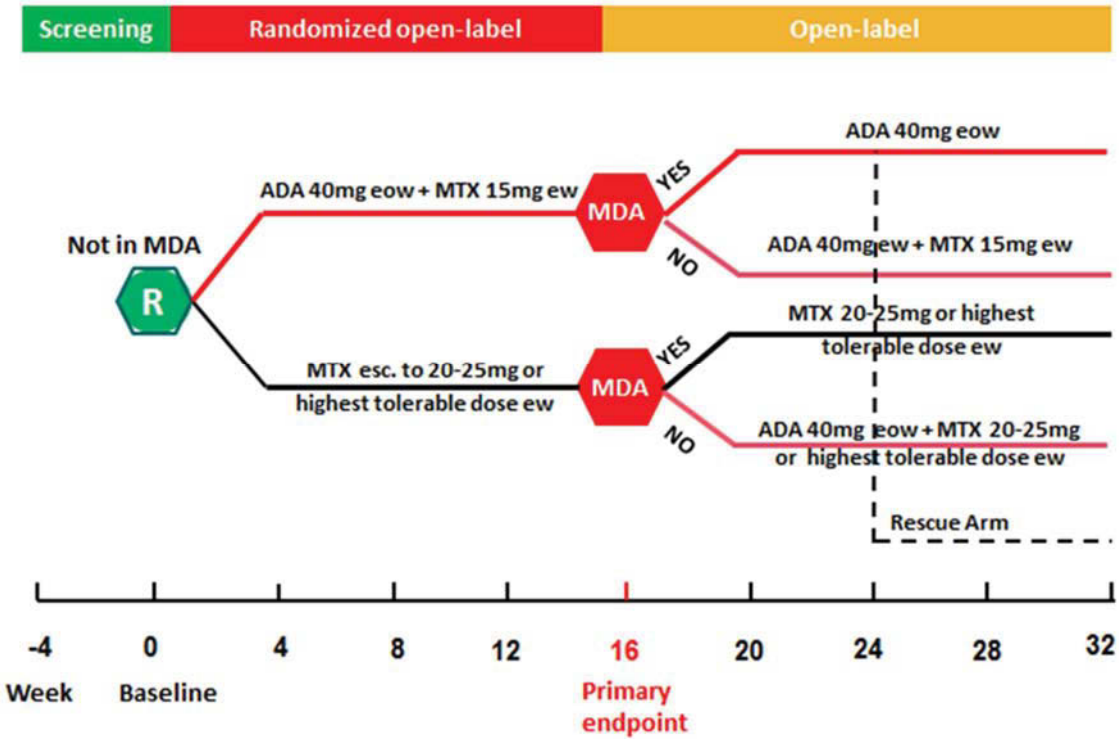
- Arm 1/Part 2: Subjects achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have MTX completely withdrawn at Week 16 and continue receiving adalimumab as monotherapy (adalimumab 40 mg eow),
- Arm 2/Part 2: Subjects not achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have adalimumab escalated to 40 mg ew in combination with MTX 15 mg ew (adalimumab 40 mg ew plus MTX 15 mg ew),
- Arm 3/Part 2: Subjects achieving MDA at Week 16 on MTX escalated to 20 – 25 mg or highest tolerable dose ew, will continue with the same MTX dose (MTX 20 – 25 mg or highest tolerable dose ew),
- Arm 4/Part 2: Subjects not achieving MDA at Week 16 on MTX escalated to 20 – 25 mg or highest tolerable dose ew, will receive adalimumab 40 mg eow in combination with MTX 20 – 25 mg or highest tolerable dose ew (adalimumab 40 mg eow plus MTX 20 – 25 mg or highest tolerable dose ew).

Subjects in Arms 1-4 of Part 2 of the study will have the option of being rescued, starting at Week 24 and based on the subject not achieving MDA and the Investigator's judgment. The selection of the rescue treatment regimen will be at the discretion of the Investigator, but should involve adalimumab and/or MTX and should not involve prohibited medications per the protocol. The recommended rescue treatment regimens are as follows:

- Subjects not achieving MDA on adalimumab 40 mg eow (Arm 1) have MTX 15 mg ew added,
- Subjects not achieving MDA on adalimumab 40 mg ew + MTX 15 mg ew (Arm 2) have MTX escalated to 20 – 25 mg ew,
- Subjects not achieving MDA on MTX 20 – 25 mg or highest tolerable dose ew (Arm 3) have adalimumab 40 mg eow added,
- Subjects not achieving MDA on adalimumab 40 mg eow + MTX 20 – 25 mg or highest tolerable dose ew (Arm 4) have adalimumab escalated to 40 mg ew.

Methodology (Continued):

A schematic of the study design is shown in the following figure:



Both adalimumab and MTX will be provided as study drugs.

MTX will be provided as a study drug for either oral or subcutaneous (sc) administration. The route of MTX administration can be selected at the discretion of the Investigator and may be exchanged between oral and sc at any time during the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, ≥ 18 years of age at Screening
2. PsA diagnosis established at least 4 weeks prior to the date of the Screening visit and confirmed by C1ASsification of Psoriatic Arthritis (CASPAR) criteria at the Screening visit
3. Not in MDA at the time of screening, defined as not meeting at least 5 of the following 7 criteria:
   - Tender joint count (TJC) ≤ 1 out of 68 assessed
   - Swollen joint count (SJC) ≤ 1 out of 66 assessed
   - PASI ≤ 1 or Body Surface Area (BSA) ≤ 3
   - Patient's assessment of pain visual analogue scale (VAS) ≤ 15

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

Main Inclusion (Continued):

- Patient's global assessment of disease activity (PtGA) VAS ≤ 20
- HAQ-DI score ≤ 0.5
- Tender entheseal points ≤ 1 out of 8 assessed

4. Has active arthritis defined as fulfilling both the below criteria at screening and baseline visits:
   - ≥ 3 tender joints (out of 68 assessed)
   - ≥ 3 swollen joints (out of 66 assessed)
5. Treated with MTX 15 mg ew for PsA defined as:
   - Oral or subcutaneous (sc) administration of MTX for at least 4 weeks prior to screening,
   - Change of the MTX administration route (oral or sc) is permitted in this time period if the administered dose of MTX 15 mg ew is not changed,
   - This is the first course of MTX the subject has been receiving for the treatment of PsA,
   - Subject has not received a dosage of MTX higher than 15 mg ew prior to the screening visit
   - Subject could have been receiving MTX doses lower than 15 mg ew before reaching the stable dose of MTX 15 mg ew defined above,
   - If the subject had been on MTX 15 mg ew for ≥ 12 weeks, temporary MTX discontinuation or dose decrease below 15 mg ew for up to 4 weeks is allowed.
6. If subject is receiving concomitant oral corticosteroids, prednisone or equivalent must be ≤ 10 mg/day and the dose must be stable for at least 1 week prior to the baseline visit.
7. If subject is receiving nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX) 2 selective inhibitors, paracetamol (up to the maximum recommended dose in the local country label), the dose must be stable for at least 1 week prior to the Baseline Visit
8. If subject is receiving other csDMARDs in addition to MTX (i.e., sulfasalazine), the dose must be stable for at least 4 weeks prior to the baseline visit. If csDMARDs are discontinued before study enrollment, the discontinuation must occur at least 4 weeks prior to the baseline Visit.
   - Leflunomide should be discontinued at least 4 weeks prior to the baseline visit.

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Has contraindication(s) to adalimumab therapy and/or known hypersensitivity to adalimumab or its excipients (refer to SmPC or prescribing information)
2. Has history of MTX intolerance/toxicity
3. Has medical condition(s) precluding MTX dose increase above 15 mg ew
4. Has had prior exposure to any tumor necrosis factor (TNF) inhibitor, other mechanism of action biologic DMARD (bDMARD) or any systemic biologic agent in general

Investigational Product:	Adalimumab, solution for injection 50 mg/mL (40 mg/0.8 mL) pre-filled syringe (PFS)
Doses:	40 mg administered eow or ew
Mode of Administration:	Subcutaneous (sc) injection
Reference Therapy:	Methotrexate Tablets: 5 mg Methotrexate Pre-filled PEN: 15 mg/0.30 ml 20 mg/0.40 ml 25 mg/0.50 ml
Dose:	Methotrexate ew
Mode of Administration:	Orally or sc
Duration of Treatment: Up to 32 weeks	

Criteria for Evaluation:

Effectiveness:

Primary Endpoint

The proportion of subjects in MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew as compared with subjects on MTX alone escalated to 20-25 mg or highest tolerable dose ew.

Secondary Endpoints

- The following outcomes after 16 Weeks of treatment with adalimumab 40 mg eow plus MTX 15 mg ew compared with MTX alone escalated to 20-25 mg or highest tolerable dose ew:
  - Change in PASDAS from baseline
  - Change in DAPSA score from baseline
  - Change in PsAID score from baseline
  - Proportion of subjects achieving ACR 20/50/70 response
  - Change in DAS28-CRP score from baseline
  - Proportion of subjects achieving PASI 75/90/100 response among subjects with BSA ≥ 3%
  - Change in HAQ-DI score from baseline
  - Changes in total SF-36 score, PCS and MCS from baseline
  - Change in DLQI score from baseline
  - Change in Leeds Enthesitis Index (LEI) from baseline
  - Change in tender dactylitic digit count from baseline
- The proportion of subjects in MDA at Week 32 on each of the four different treatment regimens (Arms 1 – 4) in Part 2 of the study.

Exploratory Endpoints:

Clinical Effectiveness

Clinical effectiveness outcomes listed under the secondary endpoints will be analyzed at Week 32 as exploratory endpoints on the 4 different treatment regimens (Arms 1-4) in Part 2 of the study.

Criteria for Evaluation (Continued):

Ultrasound

- The change in Global OMERACT-EULAR synovitis score (GLOESS) from baseline to Week 16 in subjects who had adalimumab introduced compared with those who had MTX escalated to 20 – 25 mg or highest tolerable dose ew.
- The change in OMERACT enthesitis score from baseline to Week 16 in subjects who had adalimumab introduced compared with those who had MTX escalated to 20 – 25 mg or highest tolerable dose ew.
- The change in Global OMERACT-EULAR synovitis score (GLOESS) from Week 16 – 32 in the 4 arms of Part 2 of the study.
- The change in OMERACT enthesitis score from Week 16 – 32 in the 4 arms of Part 2 of the study.

Pharmacokinetic and Immunogenicity: For subjects receiving adalimumab, blood samples will be collected for determination of adalimumab serum concentrations and the presence of anti-adalimumab antibodies (AAA).

Exploratory Research Variables and Validation Studies (Optional): Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to: nucleic acids, proteins, lipids or metabolites.

Safety: 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.

Statistical Methods:

Effectiveness: The primary and secondary efficacy endpoints will be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication. Unless otherwise stated, all statistical tests will be conducted at $\alpha = 0.05$ level (2-sided). A Week 16 database lock is planned when all randomized subjects have completed Week 16 (Part 1) of the study and statistical comparisons for the primary and secondary efficacy endpoints will be performed at Week 16 between the Part 1 treatment groups. No multiplicity adjustment will be performed for the statistical testing.

To account for missing data for the binary effectiveness endpoints, a non-responder imputation approach (NRI) will be used, e.g., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder. For continuous endpoints, the Mixed-effects Model Repeated Measures (MMRM) analysis based on all observed data will be used.

Statistical Methods (Continued):

Effectiveness (Continued):

The response rates for the primary endpoint will be compared between the treatment groups using a Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor, the duration of prior MTX use of ≤ 3 months or > 3 months. The primary analysis will be based on NRI and the sensitivity analysis will be based on OC.

Binary secondary endpoints in Part 1 will be analyzed using a similar method as the primary endpoint. Change from baseline in continuous secondary endpoints will be analyzed using MMRM with treatment, stratification factor of duration of prior MTX use, visit, and treatment-by-visit interaction as fixed effects, subject as random effect and baseline value as a covariate.

Pharmacokinetic and Immunogenicity: Adalimumab serum trough concentrations will be summarized by treatment arm at each time point using descriptive statistics including number of subjects, number of non-missing observations (nnmiss), 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. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F).

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

Ultrasound: For the analysis of ultrasound endpoints in Part 1, similar MMRM model as described for the continuous secondary endpoints will be used and baseline weight will be included as an additional covariate in the MMRM model.

Safety: Safety analyses will be carried out using safety population, which includes all subjects that received at least one dose of study medication. Treatment-emergent 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, and up to within 70 days after the last dose of the study medication. All treatment emergent AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®). The number and percent of subjects experiencing AEs will be tabulated by system organ class and preferred term. In addition, a summary of AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, which lead to premature study discontinuation will be listed and described in detail. Adverse events of special interest (AESI) will also be tabulated.

Statistical Methods (Continued):

Safety:

Observed values of vital signs and laboratory variables at each visit will be summarized for all treated subjects, and change from baseline in selected lab variables will be compared between treatment groups using a one way ANOVA. The last evaluation prior to the first dose of study drug will be used as Baseline for the analyses in Part 1. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) (Version 3) of Grade 3 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variables.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AAA	Anti-Adalimumab Antibodies
ACR	American College of Rheumatology Criteria
AEs	Adverse events
AESI	Adverse event of special interest
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
BCG	Bacillus Calmette-Guérin vaccination
bDMARDS	Biologic disease modifying anti-rheumatic drugs
BSA	Body surface area
CASPAR	ClASsification of Psoriatic Arthritis
CDC	Center for Disease Control and Prevention
CL/F	Focus on apparent clearance
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRP	C-reactive protein
CS	Clinically Significant
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
CTC	Common Toxicity Criteria
CV	Coefficient of variation
CXR	Chest X-ray
DAPSA	Disease Activity in Psoriatic Arthritis Score
DAS28	Disease Activity Score 28
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRFs	Electronic case report forms
EDC	Electronic data capture
EMA	European Medicines Agency
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HBV	Hepatitis B Virus

HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1 sub-class
IGRA	Interferon-Gamma Release Assay
IMP	Investigational Medicinal Product
INH	Isoniazid
IRB	Independent Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LEI	Leeds Enthesitis Index
LOCF	Last Observation Carried Forward
LOQ	Limit of quantification
MCS	Mental Component Summary
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed-effects Model Repeated Measures
MTX	Methotrexate
NCS	Not Clinically Significant
NNMISS	Number of non-missing observations
NRI	Non-responder Imputation
NSAIDS	Non-steroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PD	Premature Discontinuation
PDUS	Power Doppler Ultrasound
PhGA	Physician's Global Assessment of Disease Activity
PK	Pharmacokinetic

PROs	Patient reported outcomes
PsA	Psoriatic Arthritis
PsAID	Psoriatic Arthritis Impact of Disease Score
PsARC	Psoriatic Arthritis Response Criteria
PtGA	Patient's Global Assessment of Disease Activity
QoL	Quality of Life
RA	Rheumatoid Arthritis
SAP	Statistical Analysis Plan
SAPS	Self-Assessment of Psoriasis Symptoms
SC	Subcutaneous
SF-36	Short Form Health Survey 36
SH	Synovial hypertrophy
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2T	Treat-to-Target
TA MD	Therapeutic Area Medical Director
TJC	Tender Joint Count
TNF	Anti-tumor necrosis factor
ULN	Upper limit of normal range
US	Ultrasound
V/F	Volume of distribution
VAS	Visual Analogue Scale
WBC	White blood count
WHO	World Health Organization

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

3.1 Overview of Disease and its Treatment

Psoriatic arthritis (PsA) is an inflammatory progressive arthritis occurring in around 30% of patients with psoriasis and an estimated prevalence of 0.1%-0.25% in the general population.[1-4] PsA entails diverse dermatological, musculoskeletal and extraarticular manifestations that often result in impaired physical function, decreased quality of life and work disability.[5,6] Almost one third of PsA patients may have evident radiographic damage at their first presentation to the clinic and around 50% may develop erosions within 2 years of the diagnosis.[7] The burden of PsA for the patient and society is amplified by frequent comorbidities, in particular cardiovascular, resulting in an increased and premature mortality.[8]

Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) remain the cornerstone of treating PsA in clinical practice, despite their limited efficacy in reducing clinical signs and symptoms and lacking or unproven ability to inhibit radiographic progression in this disease[9,10] CsDMARDs are also recommended prior to biologic DMARDs (bDMARDs) by the international and national PsA management recommendations, unless poor prognostic factors, enthesitis, dactylitis or axial involvement are present.[11-13] In patients that failed csDMARD therapy, bDMARDs have demonstrated significant improvements in musculoskeletal and psoriasis outcomes as well as potent inhibition of radiographic progression.[13,14]

3.1.1 Methotrexate in Psoriatic Arthritis

The recommended first choice csDMARD in PsA is methotrexate (MTX).[11,12] According to the clinical practice insights, MTX may be prescribed in up to 90% of PsA patients prior to a biologic agent.[15] However, evidence for the efficacy of MTX in PsA is scant and data on the efficacious dose conflicting.

A 6-month double-blind randomized placebo controlled trial (MIPA) with a target MTX dose of 15 mg/week did not show a superiority of MTX over placebo in controlling PsA

arthritis.[16] Statistically significant improvements were only observed in patient and physician global assessments and mean Psoriasis Area and Severity Index (PASI) score, but not in the primary outcome of Psoriatic Arthritis Response Criteria (PsARC), or secondary outcomes tender and swollen joint count, composite scores for joint activity and improvement, skin improvement, measures of pain and function or laboratory inflammatory markers.[16] The trial has been criticized for several methodological drawbacks, including the low MTX dose capped at 15 mg/week.[13,14] By contrast, the open-label randomized RESPOND study in relatively early, MTX-naive PsA patients that compared infliximab in combination with MTX 15 mg/week with MTX monotherapy at the same dose, showed a better effectiveness of the biologic combination, but MTX alone provided for high joint and skin responses at Week 16 too.[17] In the recent post-hoc analysis within TICOPA, the first Treat-to-Target (T2T) trial in PsA, 40.8% and 22.4% of early PsA subjects achieved a 20% improvement in the American College of Rheumatology Criteria (ACR20) and Minimal Disease Activity (MDA) status, respectively, at Week 12 on MTX alone. Furthermore, 24.7% of subjects in the tight control arm received only MTX and remained consistently in MDA until the end of the trial at Week 48. Improvements were also seen in PASI, nail involvement, enthesitis and dactylitis.[18] Still, the majority of PsA patients will likely be insufficiently controlled on MTX alone and inhibition of radiographic progression with MTX remains unproven.[9,10]

MTX dosing in PsA is mainly based on clinical experience and evidence from trials in rheumatoid arthritis (RA). The recommended target dose is 15-25 mg weekly,[11-13] though poor tolerance seems to be common at higher MTX doses.[19] A vast majority, 91% and 83% of subjects however reached a MTX dose of at least 20 and 25 mg/week, respectively, by Week 12 in the tight control arm of TICOPA trial, following an intense MTX escalation scheme. A trend towards better outcomes with the doses higher than 15 mg/week was observed, but the differences were not significant. The interpretation of this data is however difficult due to confounding present in the dose escalation.[18]

Although the mean MTX dose has increased over the past few decades, it was still 16.2 mg/week only in the period between 1994 and 2004 in a Canadian tertiary clinic.[20]

In a more recent large German post-marketing observational study, PsA subjects eligible for biologic therapy were on a mean of 15.4 mg/week of MTX at enrolment.[15] Likewise, the mean MTX dose at baseline in the recent clinical trials with new compounds in PsA ranged between 15.8-17.5 mg/week.[21-23] This implies that in clinical practice PsA patients are insufficiently treated for prolonged periods of time with MTX doses lower than the recommended target dose.

It is also unclear whether MTX concomitant to anti-tumor necrosis factor (TNF) therapy provides an additional benefit in PsA patients that failed MTX. No difference in the efficacy of anti-TNFs with or without MTX was found for peripheral arthritis in randomized controlled trials, though there was some hint that concomitant MTX may decrease the progression of structural damage. The trials were however not designed and powered to answer this question. Data from registries suggest that the use of concomitant MTX may prolong drug survival of anti-TNFs, especially monoclonal antibodies, but that was not a consistent observation either.[24]

3.1.2 Treat-to Target in Psoriatic Arthritis

The T2T recommendations for spondyloarthritis (SpA) suggested remission, alternatively low disease activity, as the ultimate treatment goal. It has also been noted that a maximum of 6 months for reaching remission or low disease activity seems appropriate, but it is advisable to adapt therapy earlier if no significant reduction of disease activity is observed within 3 months.[25] MDA, which corresponds to the concepts of both remission and low disease activity, was suggested as a feasible treatment target in PsA.[25,26]

The first T2T trial in SpA TICOPA demonstrated that a T2T approach in comparison with the standard of care improves long-term joint and skin outcomes in subjects with early PsA.[27] Per protocol, the tight control arm mandated treatment escalation every 3 months if MDA was not achieved, starting with MTX, increasing it up to 25 mg/week within 3 months, followed by MTX combination with sulphasalazine, before an anti-TNF could be introduced. At 48 weeks (end of the trial), 39% of subjects in the tight control arm were on biologics compared with 7% in the standard care arm with no pre-defined

treatment protocol.[27] It may be speculated that the results of T2T could further be improved by an earlier anti-TNF introduction.

3.1.3 Adalimumab Overview

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 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-β).

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 for the treatment of patients with RA in the United States in December 2002 and in the European Union (EU) in September 2003. In addition, adalimumab is approved for the treatment of patients with early RA, polyarticular juvenile idiopathic arthritis (2 years of age and older), PsA, ankylosing spondylitis, Crohn's disease (adult and pediatric), ulcerative colitis, plaque psoriasis (adult), hidradenitis suppurativa in the EU, US, and the rest of the world. Adalimumab is also approved for the treatment of patients with pediatric enthesitis related arthritis (6 years of age and older), pediatric plaque psoriasis (4 years of age and older), and non-radiographic axial SpA in the EU and several other countries, as well as for intestinal Behçet's disease in

Japan, Argentina, Korea, and Taiwan. Additional updates regarding approved indications can be found in the current edition of the Humira Investigational Drug Brochure.

The efficacy and safety of adalimumab in PsA was originally demonstrated in the ADEPT trial (Study M02-518), which was a multicountry, 24-week randomized, double-blind, placebo controlled trial that compared adalimumab 40 mg subcutaneously (sc) every other week (eow) versus placebo in 313 subjects with moderately to severely active PsA and history of inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs). Significantly better results in subjects treated with adalimumab compared with placebo were seen at Weeks 12 and 24 for joint and skin outcomes, physical function and quality of life.[28,29] Subjects treated with adalimumab also experienced less radiographic progression, including its components joint space narrowing and joint erosions.[28] These improvements were sustained through the subsequent 120 weeks of open-label adalimumab therapy.[30-32] The results were confirmed in a smaller, 12-week randomized, placebo controlled trial conducted in 100 subjects with active, moderate to severe PsA who had failed csDMARD therapy. Subjects treated with adalimumab 40 mg eow had significantly improved joint and skin symptoms, physical function and quality of life versus placebo at Week 12. The improvements were sustained during open-label adalimumab therapy until Week 24.[33]

In a post-hoc analysis of the ADEPT trial, significantly more subjects achieved MDA on adalimumab than placebo at Week 24: 39% vs. 7%, respectively.[34] ADEPT subanalyses also indicated that adalimumab monotherapy provides similar results to adalimumab with concurrent MTX.[29,30]

No published data are currently available on the efficacy of adalimumab escalated to 40 mg sc every week (ew) in PsA patients that had not achieved sufficient disease control on adalimumab at the standard dose of 40 mg sc eow.

3.2 Rationale for the Study

CsDMARDs are the foundation of PsA treatment, despite their limited efficacy in reducing clinical signs and symptoms and lacking or unproven ability to inhibit radiographic progression in this disease. In subjects that failed csDMARD therapy, bDMARDs have demonstrated significant improvement in musculoskeletal and psoriasis outcomes as well as potent inhibition of radiographic progression.[9-14]

MTX is the most commonly prescribed csDMARD in PsA, but its recommended dosing has been extrapolated from clinical trials in RA and the dose-effect relationship in PsA is unclear.[13-15,18] Data suggests that even with intense MTX dose escalation to the target dose of 25 mg ew in the context of a clinical trial, the majority of PsA subjects do not achieve adequate disease control on MTX alone.[18,27] In clinical practice, PsA patients seem to be insufficiently treated for prolonged periods of time with MTX doses lower than the recommended target dose of 20-25 mg ew, and T2T principles are generally not followed.[15,21-23,25,26]

Scientific substantiation that an early introduction of bDMARD therapy substantially improves long-term outcomes in subjects with PsA is missing.[11-13] A recent post-hoc analysis of the PRESTA trial provided some evidence by showing that subjects having been treated with etanercept within 2 years of PsA duration experienced greater improvements in arthritis related scores and patient reported outcomes (PROs) than those with more than 2 years of PsA.[35]

Treatment strategy trials are clearly needed to define the best timing of bDMARD introduction, as highlighted in the recent EULAR research agenda for PsA.[11]

The present Study M14-496 (CONTROL) primarily aims to assess the effectiveness of adalimumab introduction compared with MTX dose escalation to the highest recommended dose of 20-25 mg ew[11,27] or the highest tolerable dose up to 25 mg ew in PsA subjects whose disease activity has been insufficiently controlled after an initial course of MTX at 15 mg ew. The primary effectiveness outcome will be achievement of

MDA. A possible impact of the duration of MTX therapy prior to study enrolment will be addressed by stratifying patients at randomization into those having been on MTX 15 mg ew for 3 months or less and those more than 3 months on MTX 15 mg ew.

Additionally, the maintenance or attainment of MDA on four different potential treatment optimization regimens, using adalimumab and/or MTX will be evaluated in the second part of the study. These treatment regimens include adalimumab monotherapy, adalimumab escalation to weekly dosing, delayed introduction of adalimumab and continuous treatment with MTX at the highest recommended dose of 20-25 mg or highest tolerable dose up to 25 mg ew, depending on the treatment regimen and achievement of MDA at the end of the first part of the study. Such treatment regimens are currently used in clinical practice, but lack evidence base. In subjects not achieving MDA during the second part of the study, there will be rescue treatment option in order to allow for their improved outcomes by the end of the study.

CONTROL is a treatment strategy trial in the T2T context with MDA as the major outcome of interest.

3.3 Differences Statement

This is the first study in general aiming to assess the effectiveness of bDMARD introduction compared with MTX dose escalation to the highest recommended dose of 20-25 mg ew[11,27] or the highest tolerable dose in PsA subjects who have previously been treated with MTX.

3.4 Benefits and Risks

This is a pragmatic study that will address some of the crucial data gaps in the treatment of PsA. Results are expected to inform treatment recommendations and clinical practice. The main specific benefit will be provision of data on the effectiveness of bDMARD (adalimumab) introduction in combination with MTX compared with prolonging and escalating MTX alone to the highest recommended[11,27] or tolerable dose. The other benefits will be insights into the effectiveness of different potential treatment optimization

regimens consisting of adalimumab and/or MTX in the maintenance or attainment of the outcomes in the second part of the study. These treatment regimens are used in clinical practice but lack scientific evidence.

Adalimumab has a well-established safety profile in PsA and other approved indications. Adalimumab will be administered in this study at the approved dosing regimen for PsA (i.e., 40 mg sc eow).[36,37] The only exception will be subjects not achieving MDA on the approved adalimumab dosing in combination with MTX, who will be required to escalate adalimumab to 40 mg sc ew in combination with MTX. Adalimumab 40 mg ew has been used in ACR20 non-responders in the open-label extension of the ADEPT trial through Week 144 with no increased risk of adverse events (AEs) noted.[30,31] Adalimumab has been approved in the EU for weekly dosing in psoriasis patients with inadequate response after 16 weeks of treatment.[36] Adalimumab may be used with or without concomitant MTX in PsA according to the label.[36,37]

MTX is an established immunosuppressive drug and has become the most commonly used csDMARD in inflammatory arthritides over the past decades. It is labelled for the treatment of RA and severe psoriasis across the world, and also for severe PsA in adults in some countries, like the United Kingdom.[38,39] MTX is recommended as the first-choice csDMARD by the international PsA management recommendations,[11] and is also the most commonly prescribed csDMARD in PsA.[13-15]

More than 30,000 subjects participating in hidradenitis suppurativa, polyarticular juvenile idiopathic arthritis, pediatric enthesitis related arthritis, Crohn's disease, pediatric Crohn's disease, psoriasis, pediatric psoriasis, rheumatoid arthritis, ankylosing spondylitis, non-radiographic axialspondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis, intestinal Behçet's disease, uveitis and ulcerative colitis clinical studies have been treated with adalimumab.

The majority of side effects experienced following administration of adalimumab were mild to moderate in severity.

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.

Serious adverse reactions have been reported for Humira. TNF-antagonists, such as Humira affect the immune system and their use may affect the body's defense against infection and cancer. Fatal and life-threatening infections (including sepsis, opportunistic infections and TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have also been reported with use of Humira.

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia, aplastic anaemia, central and peripheral demyelinating events and reports of lupus, lupus-related conditions and Stevens-Johnson syndrome.

Humira is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of its excipients;
- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections;
- Moderate to severe heart failure (NYHA class III/IV).

In its Summary of Product Characteristics, Special warnings and precautions for use for Humira are the following:

- Infections
  - Patients taking TNF-antagonists are more susceptible to serious infections.
  - Impaired lung function may increase the risk for developing infections.
- Serious infections
  - Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving Humira.

- Tuberculosis
  - Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving Humira. Reports included cases of pulmonary and extra-pulmonary (i.e., disseminated) tuberculosis.
- Other opportunistic infections
  - Opportunistic infections, including invasive fungal infections have been observed in patients receiving Humira. These infections have not consistently been recognised in patients taking TNF antagonists and this resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.
- Hepatitis B reactivation
  - Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e., surface antigen positive).
- Neurological events
  - TNF-antagonists including Humira have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome.
- Allergic reactions
  - Serious allergic reactions associated with Humira were rare during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. Reports of serious allergic reactions including anaphylaxis have been received following Humira administration.
- Immunosuppression
  - In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B-, NK-cells, monocyte/macrophages, and neutrophils.

- Malignancies and lymphoproliferative disorders
  - In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare.
- Haematologic reactions
  - Rare reports of pancytopaenia including aplastic anaemia have been reported with TNF-antagonists.
  - Adverse events of the haematologic system, including medically significant cytopoenia (e.g., thrombocytopaenia, leucopaenia) have been reported with Humira.
- Vaccinations Patients on Humira may receive concurrent vaccinations, except for live vaccines.
- Congestive heart failure
  - In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira.
- Autoimmune processes
  - Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long term treatment with Humira on the development of autoimmune diseases is unknown.
- Concurrent administration of biologic DMARDS or TNF-antagonists
  - Concomitant administration of adalimumab with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions.
- Elderly patients
  - The frequency of serious infections among Humira treated subjects over 65 years of age (3.6%) was higher than for those under 65 years of age (1.4%).

- Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly.

- Surgery
  - There is limited safety experience of surgical procedures in patients treated with Humira.

The SmPC states that the long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Humira should be closely monitored for infections, and appropriate actions should be taken.

The study will be conducted in subjects previously treated with MTX for PsA at 15 mg ew for at least 4 weeks. Thus, enrolled subjects will have already been exposed to MTX. For subjects randomized into the MTX escalation arm, a dose increase up to 20-25 mg ew will be required, which is the highest recommended dose in PsA[11,27] and also approved dose for PsA.[38] Rapid MTX dose escalation in subjects with PsA up to 25 mg ew has been studied before, though with a different research objective. The majority, 91% and 83% of patients were able to reach the MTX dose of at least 20 and 25 mg ew, respectively, with no major safety issue.[18,27] Further, in the present study subjects are allowed to de-escalate to the highest tolerable MTX dose in the case of suspected MTX toxicity or intolerance.

3.5 Safety Information

Adalimumab therapy has a well-established and well described safety profile based on extensive postmarketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for RA. 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. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Summary of Product Characteristics (SmPC) or prescribing information. 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 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.

The most relevant undesirable effects of MTX therapy are suppression of the haematopoietic system and gastrointestinal disorders. For a detailed description of the MTX safety profile, the Investigator should refer to the MTX prescribing information provided.

4.0 Study Objectives

4.1 Primary Objective

The primary objective is to compare the effectiveness based on the achievement of MDA at Week 16 between subjects who had adalimumab introduced and those that had MTX escalated to the highest recommended dose of 20-25 mg ew or highest tolerable dose up to 25 mg ew after inadequate disease control on the initial MTX therapy.

4.2 Secondary Objectives

The secondary objectives are:

- To compare the effectiveness at Week 16 between subjects who had adalimumab introduced and those that had MTX escalated to the highest recommended dose of 20-25 mg ew or highest tolerable up to 25 mg ew based on the following clinical, functional and quality of life measures:
  - Psoriatic Arthritis Disease Activity Score (PASDAS)
  - Disease Activity in Psoriatic Arthritis (DAPSA) score

- Psoriatic Arthritis Impact of Disease (PsAID) score
- American College of Rheumatology criteria (ACR)
- Disease Activity Score 28 (DAS28)
- Psoriasis Area and Severity Index (PASI)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- Short Form Health Survey 36 (SF-36) scores: total, physical component summary (PCS) and mental component summary (MCS)
- Dermatology Life Quality Index (DLQI)
- Leeds Enthesitis Index (LEI)
- Tender dactylitic digit count

- To evaluate the achievement of MDA at Week 32 on each of the four different treatment regimens involving adalimumab and/or MTX in Part 2 of the study.

The study also has the following **Exploratory Objectives:**

- To evaluate the effectiveness at Week 32 based on the clinical, functional and quality of life measures described under the secondary objectives on each of the four different treatment regimens involving adalimumab and/or MTX in the second part of the study.
- To evaluate ultrasound detected synovitis and enthesitis at joint and enthesis level, and treatment effect on each of the study treatment regimens.
- To assess the pharmacokinetic and immunogenicity of adalimumab with and without concomitant MTX.
- To investigate various biomarkers and their associations with treatment responses and outcomes.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This interventional Phase 4 open-label, randomized, controlled, parallel-group, multicenter study will be conducted in two (2) parts, each of 16-week duration.

Part 1 (Day 1-Week 16) is designed to compare the achievement of MDA on adalimumab introduced in combination with MTX versus MTX alone escalated to the highest recommended dose of 20-25 mg ew[11,27] or highest tolerable dose up to 25 mg ew, whatever feasible, in PsA subjects inadequately controlled after the initial course of MTX at 15 mg ew. Part 1 will be open-label, randomized, controlled, parallel group.

Part 2 (Week 16-32) is to evaluate the effectiveness of four (4) different treatment regimens consisting of adalimumab and/or MTX in maintaining or attaining MDA, as applicable. Part 2 will be open-label, parallel group. Subjects will be assigned into the four treatment arms based on their MDA status at Week 16 and initial randomized treatment. Starting at Week 24, there will be rescue treatment option based on not achieving MDA and investigator's judgment.

Eligible male and female subjects with PsA will be selected to participate in the study according to the selection criteria.

The study will enroll approximately 240 subjects at approximately 60 sites to meet the scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Following a screening period of up to 30 days, subjects meeting the selection criteria will be randomized in a 1:1 ratio to either of the two (2) arms and treated for 16 weeks in Part 1:

- Arm 1/Part 1: Adalimumab 40 mg eow in combination with MTX 15 mg ew (ADA 40 mg eow + MTX 15 mg ew),
- Arm 2/Part 1: MTX escalated to 20-25 mg or highest tolerable dose ew (MTX 20-25 mg or highest tolerable dose ew).*
  * MTX will be escalated by increments of 5.0 mg every 2 weeks, starting at 20 mg ew as the first MTX dose on or after Day 1, depending on the subject's MTX administration schedule prior to the study. In the case of

suspected MTX intolerance or toxicity, the MTX dose may be de-escalated by 5 mg and the subject may stay on the highest tolerable MTX dose below 20-25 mg ew as described per the protocol (see Section 6.1.7, Toxicity Management). The event of MTX toxicity or intolerance must be clearly documented in source documents. MTX dose should not exceed 25 mg ew in this study.

After the assessment of MDA at Week 16 (primary endpoint), subjects will be assigned to one of the four (4) treatment arms based on the achievement of MDA and initial randomized treatment, and treated for additional 16 weeks in Part 2 as follows:

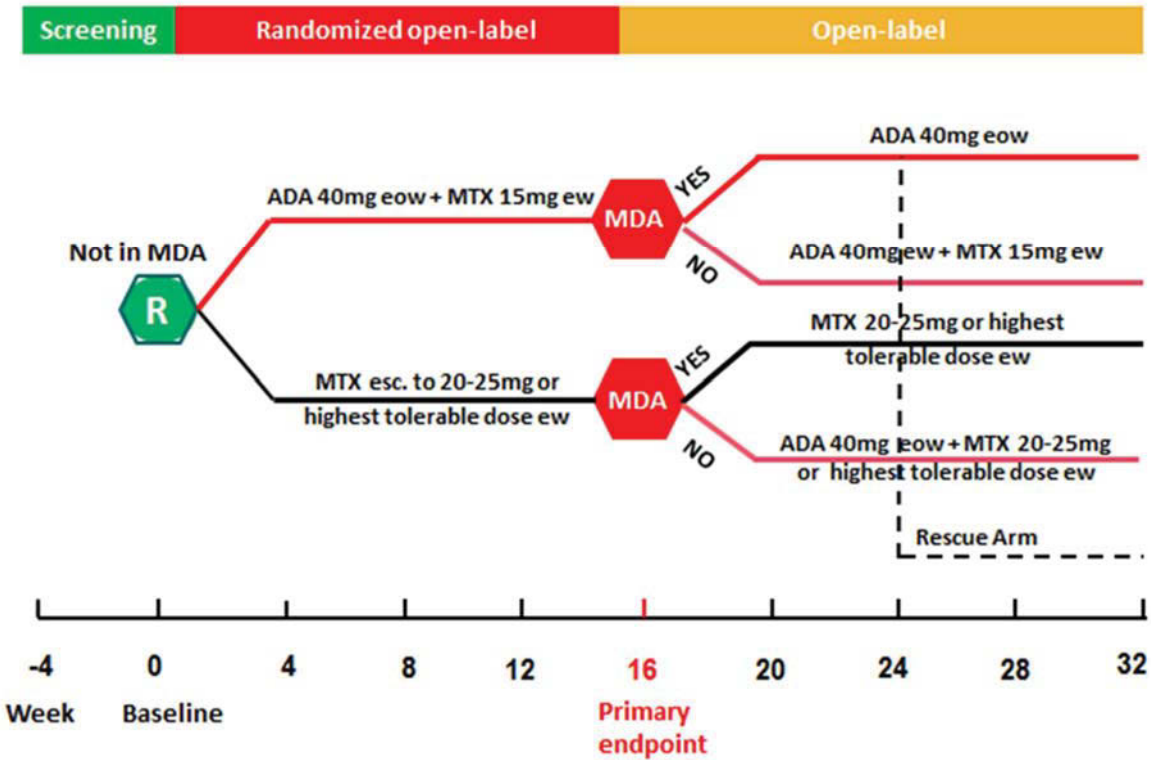
- Arm 1/Part 2: Subjects achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have MTX completely withdrawn at Week 16 and continue receiving adalimumab as monotherapy (ADA 40 mg eow),
- Arm 2/Part 2: Subjects not achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have adalimumab escalated to 40 mg ew in combination with MTX 15 mg ew (ADA 40 mg ew plus MTX 15 mg ew),
- Arm 3/Part 2: Subjects achieving MDA at Week 16 on MTX escalated to 20-25 mg or highest tolerable dose ew, will continue with the same MTX dose (MTX 20-25 mg or highest tolerable dose ew),
- Arm 4/Part 2: Subjects not achieving MDA at Week 16 on MTX escalated to 20-25 mg or highest tolerable dose ew, will receive adalimumab 40 mg eow in combination with MTX 20-25 mg or highest tolerable dose ew (ADA 40 mg eow plus MTX 20-25 mg or highest tolerable dose ew).

Subjects in Arms 1-4 of Part 2 of the study will have the option of being rescued, starting at Week 24 and based on the subject not achieving MDA and the Investigator's judgment. The selection of the rescue treatment regimen will be at the discretion of the Investigator, but should involve adalimumab and/or MTX and should not involve prohibited medications per the protocol. The recommended rescue treatment regimens are as follows:

- Subjects not achieving MDA on adalimumab 40 mg eow (Arm 1) have MTX 15 mg ew added,
- Subjects not achieving MDA on adalimumab 40 mg ew + MTX 15 mg ew (Arm 2) have MTX escalated to 20-25 mg ew,
- Subjects not achieving MDA on MTX 20-25 mg or highest tolerable dose ew (Arm 3) have adalimumab 40 mg eow added,
- Subjects not achieving MDA on adalimumab 40 mg eow + MTX 20-25 mg or highest tolerable dose ew (Arm 4) have adalimumab escalated to 40 mg ew.

A schematic of the study design is shown below in Figure 1:

Figure 1. Control Design Scheme



Both adalimumab and MTX will be provided as study drugs.

MTX will be provided as a study drug for either oral or subcutaneous (sc) administration. The route of MTX administration can be selected at the discretion of the Investigator and may be exchanged between oral and sc at any time during the study.

5.1.1 Screening Period

At the Screening Visit, subjects who provide written (signed and dated) informed consent prior to any study specific procedures, will receive a unique subject number via Interactive Response Technology (IRT) system and will undergo the study procedures identified in Section 5.3.1.1 associated with the Screening Visit. The investigator will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 during the period from the Screening Visit through Day 1 prior to dosing and record the results of this assessment and the details of the informed consent process in the subject's medical records. Eligible subjects have up to 30 days following the Screening Visit to enroll into the study. The screening period may be extended with the approval of the AbbVie TA MD for certain circumstances (e.g., due to delay of availability of screening test results, holidays or scheduling/availability issues).

5.1.1.1 Rescreening

- Subjects that initially screen fail for the study may be permitted to re-screen once. There is no minimum period of time a subject must wait to re-screen for the study. All screening procedures with the possible exceptions noted below will be repeated.
- Re-consent is required if there is a newly approved informed consent since the original screening visit or if 60 days have passed.
- If there is one exclusionary laboratory result during screening, a re-test of that one particular value is allowed without repeating all other laboratory tests provided no more than 30 days have passed since the original screening visit.
- If the subject had a complete initial Screening visit including the assessment of a PPD test (or equivalent), or QuantiFERON-TB Gold test, Chest x-ray (if applicable) and ECG, these tests will not be required to be repeated for the re-screening visit, provided the conditions noted in Section 5.2 are met and no

more than 90 days have passed since the original screening visit. Note: If the subject initiated TB treatment and the treatment was completed outside the 30 day screening window, the screening period may be extended with the approval of the AbbVie TA MD.

The subject must meet all inclusion and none of the exclusion criteria at the time of enrollment in order to qualify for the study. As appropriate, sites are encouraged to contact the AbbVie Therapeutic Area Medical Director (TA MD) to confirm if subjects should or should not be re-screened.

For subjects who do not meet the study eligibility criteria, the site personnel must register the subject as a screen failure in both IRT and electronic data capture (EDC) systems. For subjects that re-screen, the Screening number assigned by the IRT at the initial Screening visit should be used; a new Screening number should not be requested.

5.1.2 Treatment Period

5.1.2.1 Part 1 (Randomized Open Label Treatment Period)

At the Baseline visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in Section 5.2.1 and Section 5.2.2 will be enrolled into the study and randomized in a 1:1 ratio to Arm 1 or Arm 2 of Part 1 (as described in Section 5.1). During this period of the study, subjects will visit the study site at Week 2, Week 4 and then monthly through Week 16 (if local requirements ask for additional safety assessments, e.g., due to MTX treatment, respective laboratory tests should be done locally). A ± 2-day window is permitted around scheduled study visits.

IRT will be utilized to dispense the appropriate study drug (adalimumab and MTX) to subjects for administration during the visit or at the regularly scheduled day for MTX. Subjects will be given dosing instructions and a dosing diary at the Baseline visit.

5.1.2.2 Part 2 (Open-Label Treatment Period)

After completing the randomized-open label treatment period at Week 16, subjects will be assigned to Arms 1-4 of Part 2 (as described in Section 5.1), based on the achievement of MDA and initial randomized treatment, and treated for additional 16 weeks. Starting at Week 24, there will be rescue treatment option based on not achieving MDA and investigator's judgment. During this study period, subjects will visit the study site monthly through Week 32. A ± 2-day window is permitted around scheduled study visits. Subjects will be dispensed study drugs at the Week 16 Visit for administration during the visit or at the regularly scheduled day for MTX.

No study drug will be administered or injected after the final visit (Week 32 Visit). Subjects may discontinue study drug treatment at any time during study participation. Subjects who end study participation early will have a Premature Discontinuation (PD) Visit and complete the procedures outlined for the PD Visit in Appendix C as soon as possible after the last dose of study drug and preferably prior to the administration of any new therapies.

Follow-Up Period

Subjects may discontinue their study participation at any time. Subjects that end study participation early will have a PD Visit. All subjects will have a follow-up phone call 70 days (± a 7 day window) after the last administration of adalimumab to obtain information on any new or ongoing AEs. For subjects taking only MTX, the follow-up phone call will occur 70 days (± 7 day window) after the last administration of MTX.

5.2 Selection of Study Population

Approximately 240 adult subjects with active PsA (defined as not in MDA and having at least 3 tender and 3 swollen joints) despite having been treated with the first course of MTX at the dose of 15 mg ew for ≥ 4 weeks and biologic naive who meet all the inclusion and none of the exclusion criteria are planned to be enrolled in the study at approximately 60 sites.

5.2.1 Inclusion Criteria

1. Adult male or female, ≥ 18 years of age at Screening.
2. PsA diagnosis established at least 4 weeks prior to the date of the Screening visit and confirmed by CASPAR criteria at the Screening visit
3. Not in Minimal Disease Activity (MDA) at the time of screening, defined as not meeting at least 5 of the following 7 criteria:
   - Tender joint count (TJC) ≤ 1 out of 68 assessed
   - Swollen joint count (SJC) ≤ 1 out of 66 assessed
   - PASI ≤ 1 or body surface area (BSA) ≤ 3
   - Patient's assessment of pain visual analogue scale (VAS) ≤ 15
   - Patient's global assessment of disease activity (PtGA) VAS ≤ 20
   - HAQ-DI score ≤ 0.5
   - Tender entheseal points ≤ 1 out of 8 assessed
4. Has active arthritis defined as fulfilling both the below criteria at screening and baseline visits:
   - ≥ 3 tender joints (out of 68 assessed)
   - ≥ 3 swollen joints (out of 66 assessed)
5. Treated with MTX 15 mg ew for PsA defined as:
   - Oral or subcutaneous (sc) administration of MTX for at least 4 weeks prior to screening,
   - Change of the MTX administration route (oral or sc) is permitted in this time period if the administered dose of MTX 15 mg ew is not changed,
   - This is the first course of MTX the subject has been receiving for the treatment of PsA,
   - Subject has not received a dosage of MTX higher than 15 mg ew prior to the screening visit,
   - Subject could have been receiving MTX doses lower than 15 mg ew before reaching the stable dose of MTX 15 mg ew defined above,

- If the subject had been on MTX 15 mg ew for ≥ 12 weeks, temporary MTX discontinuation or dose decrease below 15 mg ew for up to 4 weeks is allowed.

6. If subject is receiving concomitant oral corticosteroids, prednisone or equivalent must be ≤ 10 mg/day and the dose must be stable for at least 1 week prior to the Baseline visit

7. If subject is receiving nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX) 2 selective inhibitors, paracetamol (up to the maximum recommended dose in the local country label), the dose must be stable for at least 1 week prior to the Baseline Visit

8. If subject is receiving other csDMARDs in addition to MTX (i.e., sulfasalazine), the dose must be stable for at least 4 weeks prior to the Baseline visit. If csDMARDs are discontinued before study enrollment, the discontinuation must occur at least 4 weeks prior to the Baseline Visit

   - Leflunomide should be discontinued at least 4 weeks prior to the Baseline visit

9. Subject must be able and willing to self-administer sc injections or have a qualified person available to administer sc injections

10. Laboratory values of the following at the Screening visit:

    - Hemoglobin count > 8.5 g/dL
    - White blood count (WBC) > 3.5×10^9/L
    - Platelet count > 100×10^9/L
    - Absolute neutrophil count (ANC) > 1.5×10^9/L
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels must be within 3 times the upper limit of normal range (ULN) for the laboratory conducting the test

11. Subject has a negative TB Screening Assessment. If the subject has a positive TB test or evidence of a latent TB infection, the subject must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing

TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline. (See Section 5.3.1.1)

12. Subject is judged to be in good health as determined by the Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG)

13. A negative serum pregnancy test at the Screening visit and a negative urine pregnancy test for women of childbearing potential at the Baseline visit (prior to administration of first dose of study drug). A serum pregnancy test will also be taken at the Baseline visit if the urine pregnancy test is positive. If the serum result at the Baseline visit is positive, the subject will be discontinued from the study

14. If female subject, is either not of childbearing potential (defined as postmenopausal for at least 1 year prior to Screening), or surgically sterile (bilateral salpingectomy, bilateral oophorectomy and/or hysterectomy), or is of childbearing potential and is practicing an approved method of birth control (refer to Section 5.2.4) throughout the study and for 180 days after last dose of study drug.

15. Male subjects who are sexually active with female partner(s) of childbearing potential, must agree, from Study Day 1 through 180 days after the last dose of study drug to practice the protocol specified contraception (Section 5.2.4).

    A condom without spermicide is acceptable in countries where spermicide is not available

16. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures

Rationale for the Inclusion Criteria:

1 – 9	To select the adequate subject population for this study
10 – 12	For the safety of the study subjects

13 – 15	The impact of adalimumab on pregnancies is unknown. MTX is teratogenic and may be genotoxic
16	In accordance with harmonized GCP

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Has contraindication(s) to adalimumab therapy and/or known hypersensitivity to adalimumab or its excipients (refer to SmPC or prescribing information)
2. Has history of MTX intolerance/toxicity (see MTX prescribing information)
3. Has medical condition(s) precluding MTX dose increase above 15 mg ew (as per Investigator's judgment)
4. Has had prior exposure to any TNF inhibitor, other mechanism of action bDMARD or any systemic biologic agent in general
5. Had intra-articular or parenteral administration of corticosteroids in the preceding 4 weeks of the Baseline visit. Inhaled corticosteroids for stable medical conditions are allowed
6. Was treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline visit
7. Has a history of or currently has active inflammatory articular disease other than PsA (e.g., RA, JIA, axial SpA, gout) or systemic autoimmune disease (e.g., mixed connective tissue disease, systemic lupus erythematosus, vasculitis) or currently has active fibromyalgia.
    - Subjects with a history of fibromyalgia who are asymptomatic at baseline are permitted.

8. Had joint surgery at joints to be assessed within this study within the preceding 60 days of the Baseline visit
9. Has active skin disease other than psoriasis that would interfere with the assessment of psoriasis
10. Received UVA phototherapy including PUVA or used a tanning booth 4 weeks prior to the Baseline visit
11. Received systemic psoriasis therapy (e.g., oral retinoids) within 4 weeks prior to the Baseline visit.
12. Received topical psoriasis therapy (e.g., keratolytics, coal tar, anthralin, etc.) within 2 weeks of the Baseline visit with the exception of the following:
    - Shampoos that contain no corticosteroid
    - Bland (without beta or alpha hydroxy acids) emollients
    - Low potency (Class VI or VII) topical corticosteroids on the palms, soles, face, inframammary area and groin only
13. Permanently wheelchair-bound or bedridden
14. Currently enrolled in another investigational study. Concurrent participation in non-interventional, epidemiologic or registry trials may be permitted with approval from the AbbVie TA MD
15. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study
16. Received any live/attenuated vaccine within 30 days prior to the Baseline visit, or will require vaccination during the study participation including up to 70 days after the last dose of study drug
17. Clinically significant abnormal screening laboratory results as evaluated by the Investigator
18. History of clinically significant drug or alcohol abuse within 1 year preceding the Baseline visit

19. Known HIV infection, invasive infection (e.g., listeriosis and histoplasmosis) or immunodeficiency syndrome

20. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study

21. Active HBV and HCV defined as:

    - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for Hepatitis B core antibody (HBc Ab) positive (+) subjects;
    - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab)

22. Chronic or recurring infections or active TB

23. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline visit or oral anti-infectives within 14 days prior to the Baseline visit

24. Current or history of joint infection within 2 years prior to the Baseline visit

25. Chronic infection of the upper respiratory tract (e.g., sinusitis), chest (e.g., bronchiectasic lung disease), urinary tract or skin (e.g., paronychia, ulcer, open wounds)

26. Evidence of dysplasia or malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix

27. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease

28. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident and any other condition which would put the subject at risk by participation in the study

29. Has poorly controlled underlying medical condition including cardiac, pulmonary, metabolic, renal, neurologic or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the subject at an unacceptable risk for participation in the study
30. Positive pregnancy test at Screening or Baseline Visit
31. Female subject who is pregnant, breast-feeding or considering becoming pregnant during the study or for approximately 180 days after the last dose of study drug
32. Male subject who is considering fathering a child or donating sperm during the study or for approximately 180 days after the last dose of study drug.
33. Received apremilast or JAK inhibitor within 4 weeks of Baseline.
34. Received tramadol or equivalent opioids and/or non-opioid analgesics *(e.g., tapentadol, codeine, hydrocodone)* or narcotics in fixed combination with acetaminophen not at a stable dose for at least 1 week prior to Baseline

Rationale for Exclusion Criteria

1 – 15, 33, 34	To select the adequate subject population for this study
16 – 29	For the safety of the study subjects
30 – 32	The impact of ADA on pregnancies is unknown. MTX is teratogenic and may be genotoxic.

5.2.3 Prior and Concomitant Therapy

5.2.3.1 Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving within 30 days prior to screening 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 electronic case report form (eCRF).

All prior drug therapies for PsA since the 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.

MTX use for PsA at a stable dose of 15 mg ew (oral or subcutaneous) for ≥ 4 weeks prior to Screening is required per the protocol; dates of use, dosage(s), route of administration(s) and reason for use should be documented and must be recorded on the appropriate electronic case report form (eCRF).

All subjects receiving MTX in this study are recommended to be on folic or folinic acid supplementation with the dose and regimen chosen at the Investigator's discretion. As per general guidance, folic or folinic acid should not be taken on the same day that the MTX is administered, but may be taken all other days in the week, beginning 24 hours after the MTX dose.

Oral antiemetic agents are permitted to treat transient gastrointestinal tolerability problems possibly caused by MTX dose increase. The selection of an antiemetic agent and duration of antiemetic treatment is at the discretion of the Investigator, but is not advised to exceed 2 weeks.

Concomitant csDMARDs (i.e., sulfasalazine ≤ 2 g/day) must be at a stable dose for ≥ 4 weeks before the baseline visit and are to remain stable for the duration of the study. If csDMARDs (other than MTX) are discontinued before the study, this must be done ≥ 4 weeks before the baseline visit. Leflunomide must be discontinued at least 4 weeks prior to the baseline visit and should not be used during the study.

The use of NSAIDs, including COX 2 inhibitors, paracetamol (up to the maximum recommended dose in the local country label), are allowed during the study, if subjects are receiving stable prescribed doses for ≥ 1 week before the baseline visit. 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. If taking any of the above at baseline on an as-needed basis, they should continue to use them for the same reason and same dose each time. 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. In addition, for subjects participating in the US substudy, no NSAIDs should be used within 48 hours of the scheduled US examination.

Narcotics other than tramadol or equivalent opioids and/or non opioid analgesics (including codeine), are prohibited except in fixed combination with acetaminophen. Administration of combined narcotics and acetaminophen and tramadol or equivalent opioids and/or non-opioid analgesics should remain at a stable dose and should not occur within 24 hours prior to a study visit with joint assessments.

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 for ≥ 1 week prior to baseline and remain stable throughout the study. Inhaled corticosteroids for stable medical conditions are allowed.

Doses of all the permitted concomitant medications for PsA must remain stable throughout study participation (except as medically required due to an AE (Section 6.1.1.1).

For subjects who require isoniazid (INH) for TB prophylaxis, consideration should be given to administer pyridoxine (vitamin B_6) to prevent peripheral neuropathy.

During the course of the study, subjects may continue treatment with medicated shampoos that do not contain corticosteroids, bland (without beta or alpha hydroxy acids) emollients, or Class VI or VII low-potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only (Appendix D). Application of these topical therapies for psoriasis; however, should not occur within 24 hours of a study visit where

psoriasis assessments are collected so as not to interfere with clinical assessments for psoriasis.

In addition for subjects aged ≤ 30 with a reported malignancy adverse event, prior exposure to or current use of antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant documents, 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.

Medications used to treat suspected hypersensitivity reaction or other post-dose systemic reaction will be captured as concomitant therapy.

Folic/folinic acid and any other concomitant PsA medications will be received by local prescriptions.

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

5.2.3.2 Prohibited Therapy

The following are prohibited medications during the study:

All bDMARDs (with the exception of adalimumab study drug) and other systemic biologic agents with a potential therapeutic impact on the disease being studied, including but not limited to the following:

- Etanercept (Enbrel®)
- Infliximab (Remicade®)

- Abatacept (Orencia®)
- Anakinra (Kineret®)
- Rituximab (Rituxan®)
- Natalizumab (Tysabri®)
- Tocilizumab (Actemra®)
- Golimumab (Simponi®)
- Certolizumab (Cimzia®)
- Ustekinumab (Stelara®)
- Belimumab (Benlysta®)
- Secukinumab (Cosentyx®)
- Ixekizumab (Taltz®)

The following other medications/therapies:

- Apremilast
- JAK inhibitors (examples include but are not limited to: tofacitinib (Xeljanz®), baricitinib (Olumiant®), filgotinib, upadacitinib)
- Leflunomide
- Cyclosporine A
- Corticosteroids administered by local injection or any kind of parenteral route
- Live/attenuated vaccines (during the study and for 70 days after the last dose of study drug)
- Rifampin/Pyrazinamide combination
- Anti-retroviral therapy
- Opioid analgesics (other than tramadol or equivalent opioids and/or non-opioid analgesics and narcotics in fixed combination with acetaminophen) or marijuana
- Any investigational drug of chemical or biologic nature
- UVA phototherapy including PUVA or use of a tanning booth
- Systemic psoriasis therapy (e.g., oral retinoids)

- Topical psoriasis therapy (e.g., keratolytics, coal tar, anthralin, etc.) with the exceptions of medicated shampoos that do not contain corticosteroids, bland (without beta or alpha hydroxy acids) emollients, or Class VI or VII low-potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only (Appendix D)

Medications that may have potential for drug interaction with MTX should be administered with caution and careful ongoing monitoring. Such medications include, but are not limited to:

- Phenytoin, tetracycline, nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates.
- Trimethoprim/sulfamethoxazole, co-trimoxazole
- Proton pump inhibitors (such as omeprazole).

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 (see below for subjects participating in the US substudy). If the site determines the subject has taken these medications within 12 hours prior to arrival for a study visit, the study visit should be cancelled and rescheduled.

For subjects participating the US substudy, no NSAIDs should be used within 48 hours of the scheduled US examination. If the site determines the subject has taken NSAIDs within 48 hours prior to the scheduled US evaluation, the US examination should be cancelled and rescheduled.

Subjects may be discontinued from the study if any of the above prohibited medications are used during the study. In addition, joint surgeries should not be performed during the study.

Contact the AbbVie TA MD identified in Section 6.1.5 Adverse Event Reporting, if there are any questions regarding prohibited therapy(ies).

5.2.4 Contraception Recommendations and Pregnancy Testing

Contraception Recommendation for Females

If female, subject must be either permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) or postmenopausal defined as:

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

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 180 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 90 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, excluding low-dose oral gestagens (mini-pills containing either lynestrenol or norestisteron) initiated at least 90 days prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e, Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the women of childbearing potential study participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).

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

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

Contraception Recommendation for Males

If the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree from Study Day 1 through 180 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, male subject agrees not to donate sperm from Study Day 1 through 180 days after the last dose of study drug.

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

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

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

Study procedures are discussed in detail in this section, with the exception of drug concentration measurements and antibody measurements (discussed in Section 5.3.2 and the collection of adverse event (AE) information (discussed in Section 6.0). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

At the Screening visit, the subject will sign and date a study specific, Independent Ethics Committee (IEC)/Independent Review Board (IRB) approved informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Participation in the 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 exploratory research/validation studies. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Inclusion/Exclusion Criteria

Subjects will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria at the Screening and Baseline visits.

Medical and Surgical History

A complete non-PsA medical and surgical history, including history of alcohol and tobacco use will be obtained from each subject at the Screening visit. Additionally, a list

of each subject's specific PsA related medical and surgical history should be recorded at Screening. An updated medical history will be obtained prior to study drug administration at Baseline, to ensure the subject is still eligible for enrollment, and the medical history will be updated as necessary throughout the study.

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

Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Appendix C. The physical examination at the baseline visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted by the Investigator at Baseline prior to the first dose of study drug should be recorded in the subject's medical history. Abnormalities noted after the Baseline visit and first dose of study drug should be evaluated and documented by the Investigator as to whether or not these are adverse events. All findings whether related to an adverse event or part of each subject's medical history should be captured on the appropriate eCRF page.

A symptom-directed physical examination will be performed when necessary.

Confirmation of PsA Diagnosis

The clinical diagnosis of PsA of at least 4-week duration prior to the screening date should be verified at the screening visit against the CASPAR classification criteria (40) outlined below.

CASPAR Classification Criteria	To meet the criteria of the ClASsification of Psoriatic ARthritis (CASPAR) Study Group,* a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following 5 categories: 1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.† A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified healthcare provider. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report. 2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination. 3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immuosorbent assay or nephelometry, according to the local laboratory reference range. 4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist. 5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

* Taylor W, Gladman D, Helliwell P, et al; the CASPAR Study Group. Classification criteria for psoriatic arthritis. Arthritis Rheum. 2006;54:2665-73.[40]

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, body weight, and body temperature will be obtained at each visit, as noted in Appendix C. Blood pressure, pulse rate and respiratory rate should be performed before blood draws are performed. Height will be measured at the Screening Visit only and weight will be measured at the Screening visit and Week 32 or the premature discontinuation visit (with shoes off). All measurements will be recorded in metric units where applicable.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at the designated study visits as specified in Appendix C. 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 site monitor and kept with the subject's source documents onsite.

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

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

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 90 days of Screening, provided all protocol required documentation is available at the site (as outlined below) and provided nothing has changed in the subject's medical history to warrant a repeat test.

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

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

the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Investigator must contact the AbbVie TA MD before enrolling the subject.

TB Screening

For subjects treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test) must be performed during the Screening Period for all subjects including those with a prior history of Bacille Calmette-Guérin (BCG) administration.

For subjects NOT treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month prior to TB screening), a PPD skin test (alternatively, also known as tuberculin skin test) must be placed, or an 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.

If a subject had a negative PPD or QuantiFERON-TB Gold test (or IGRA equivalent such as T-SPOT TB test) within 90 days 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. All cases where the Investigator feels a repeat test is not needed must be discussed with the AbbVie TA MD prior to subject enrollment.

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." *(If required by specific countries a two-step test may be performed per local guidelines. The result of the second test should be recorded. An induration of 5 mm or greater will be considered as PPD positive.)*

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.

If the PPD or the QuantiFERON-TB Gold 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 Center for Disease Control (CDC) 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 for at least 2 weeks (or per local guidelines, whichever is longer) prior to starting study therapy.

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 a QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test. However, only one test is required. If the QuantiFERON-TB Gold test is indeterminate, the site should repeat the test with another

blood sample or perform a PPD test. If the second QuantiFERON-TB Gold 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.

Hepatitis B Testing

All subjects will be tested for the presence of the Hepatitis B Virus (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 Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

Subjects with a negative HBs Ag test and tests showing the results below, do not require HBV DNA PCR qualitative testing.

- HBc Ab Total (–) and HBs Ab (–)
- HBc Ab Total (–) and HBs Ab (+)
- HBc Ab Total (+) and HBs Ab (+)

Hepatitis C Testing:

Blood samples for Hepatitis C serology will be obtained at the Screening Visit. A subject will not be eligible for study participation if test results indicate active Hepatitis C (HCV RNA detectable in any subject with anti HCV Ab).

Pregnancy Test

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. At the Baseline Visit, subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. A serum

pregnancy test will also be taken on Day 1 if the urine pregnancy test is positive. If the serum result at Day 1 is positive, the subject is considered a screen failure. 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.

Starting at baseline, all women of childbearing potential will have a urine pregnancy test performed locally by designated study personnel at each visit, including at the last dose and PD visit, if applicable (see Appendix C).

Clinical Laboratory Tests

Blood and urine samples will be obtained for clinical laboratory tests. Samples will be obtained at the designated study visits as specified in Appendix C. Samples will be obtained for the laboratory tests listed in Table 1.

All Screening laboratory results must be reviewed, signed and dated by the Investigator for review and signature prior to the randomization of a subject. Subjects will not be randomized into the study if laboratory or other Screening result abnormalities are deemed clinically significant by the Investigator.

When blood draws are performed as part of a clinic visit, the draws should be performed after all clinical assessments and 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 required by country regulatory authorities or considered warranted by the Investigator to confirm eligibility, subjects will be tested for antibodies to the Human

Immunodeficiency Virus (HIV) at Screening and documented that the test has been performed. This testing is to be done at a local lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

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. Laboratory abnormalities are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be an adverse event.

Table 1. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis	Other Laboratory Tests
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 Chloride Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Sodium bicarbonate	Specific gravity Ketones pH Protein Glucose Blood Leukocytes Nitrites	Serum pregnancy test Urine pregnancy test HIV, if applicable (testing to be conducted at local lab) HBsAg HBsAb HBcAb HBV PCR HCVAb HCV PCR PPD or the QuantiFERON-TB Gold test hs-CRP FSH*

* If applicable.

Assessment of Peripheral Joints

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

TJC68 and SJC66, including the DIP joints of the hands and excluding hips for swelling, will be performed as recommended for clinical trials in PsA.[41] Additionally, the TJC28 and SJC28 required for the calculation of DAS28 will be extracted from the corresponding TJC68 and SJC66, respectively. The TJC/SJC assessments will be performed at the visits specified in Appendix C.

Tender Joint Count (TJC)

An assessment of 68 joints (TJC68; Appendix E) will be done for tenderness by pressure manipulation on physical examination. Joint pain/tenderness will be classified as either present ("1"), absent ("0"), replaced ("9") or no assessment ("NA").

Swollen Joint Count (SJC)

An assessment of 66 joints (SJC66; Appendix E) will be done by physical examination. The joints to be examined for swelling are the same as those examined for tenderness, except the hip joints excluded. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9") or no assessment ("NA").

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

Dactylitis Assessment

Dactylitis will be assessed as dactylitic digit count and tender dactylitic digit count.

Hands and feet bilaterally will be assessed for the presence/absence of dactylitis and associated tenderness. The score for each dactylitic count and tender dactylitic count can range 0-20 (Appendix F). The dactylitis assessments will be performed at the visits specified in Appendix C.

Enthesitis Assessment

Leeds Enthesitis Index (LEI)

The LEI[42] is an enthesitis measure developed specifically for PsA and assesses the presence or absence of tenderness at the following 3 bilateral enthesial sites: medial femoral condyles, lateral epicondyles of the humerus, and Achilles tendon insertions. Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0-6 (Appendix G). The LEI assessments will be performed at the visits specified in Appendix C.

Tenderness at the Plantar Fascia

Tenderness at the plantar fascia as an additional typical PsA enthesitis site[27] will be assessed as present (1) or absent (0) (Appendix G). The tenderness at the plantar fascia assessment will be performed at the visits specified in Appendix C.

Psoriasis Evaluation

Psoriasis Area and Severity Index (PASI)

The PASI provides quantitative assessment of psoriasis lesional burden based on the amount of body surface area involved and degree of severity of erythema, induration, and scale, weighted by body part.[43,44] A qualified Investigator or designee who has been trained by the sponsor/designee, if necessary, will perform the PASI assessment (Appendix H). The site should make every attempt to have the same qualified Investigator or designee perform all PASI assessments on a given subject throughout the study as specified in Appendix C.

Body Surface Area (BSA)

BSA affected by psoriasis will be measured. The subject's right or left hand will be selected as the measuring device. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1% of BSA.[45] Measurement of the total area of involvement by the Investigator or delegated site staff is

aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved. BSA will be measured as specified in Appendix C.

Physician's Global Assessment of Disease Activity (PhGA)

PhGA will be evaluated on a 0-100 mm horizontal visual analogue scale (VAS) with a question referring to both musculoskeletal and skin disease activity currently[46] (Appendix I). The PhGA is to be performed at the visits described in Appendix C.

Patient Reported Outcomes (PROs)

The subject should complete these questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's responses. Subjects will be instructed to follow the instructions provided with each instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects will complete the following questionnaires at the visits specified in Appendix C.

Patient's Global Assessment of Disease Activity (PtGA)

PtGA will be evaluated on a 100 mm horizontal VAS with a question referring to both arthritis and psoriasis disease activity over the past week.[46] The VAS is anchored by the opposite adjectives of "excellent" and "poor."

Patient's Global Assessment of Arthritis

Patient's Global Assessment of Arthritis will be performed on a 100 mm horizontal VAS with a question referring to arthritis disease activity over the past week.[46] The VAS is anchored by the opposite adjectives of "excellent" and "poor."

Patient's Assessment of Pain

Patient's Assessment of Pain will be performed on a 100 mm horizontal VAS with a question referring to pain over the past week.[46] The VAS anchors are "no pain" and "pain as bad as it could be."

Psoriatic Arthritis Impact of Disease (PsAID)

PsAID is a validated patient self-reported tool to assess the impact of PsA on patient's life. Two versions of the questionnaire were developed by an European League Against Rheumatism (EULAR) initiative: one for clinical practice (PsAID-12) and one for clinical trials (PsAID-9). Both contain physical and psychological domains. The PsAID-9 version will be used in this study.[47]

Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI is a standardized measure of physical function in arthritis. The HAQ-DI questionnaire contains 20 items divided into 8 domains that measure: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities.[48]

Short Form 36 Health Survey (SF-36)

SF-36 is a generic measure to assess patients' general health and well-being (i.e., health related quality of life). The short version 2 (SF-36v2) consisting of 36 questions will be used.[49,50]

Dermatology Life Quality Index (DLQI)

DLQI is a measure of subject's quality of life (QoL) related to skin disease. The DLQI questionnaire consists of 10 questions concerning subjects' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment.[51]

Self-Assessment Psoriasis Symptoms (SAPS) v.3.0

The subject will rate his/her psoriasis symptoms within the past 24 hours utilizing an 11-item questionnaire.[52]

Musculoskeletal Ultrasound (US)

Investigators will at study start indicate if they want to participate in the optional US assessments or not. If they decide to participate, they should, if possible, perform an US evaluation for every subject they enroll at visits indicated in Appendix C.

For the sites participating in the optional US assessment, high-end ultrasound equipment is recommended. The US must be performed by an expert sonographer (rheumatologist or radiologist) with verifiable training and/or certification in ultrasonography, 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 should be blinded for subject characteristics and treatment arm; he/she should be the same person throughout the study, and a back-up with the same qualifications should be appointed.

The assessments and scoring will be locally performed. US should be performed the same day as the clinical examination, or the day before the visit if not possible, and prior to injecting study medication. The subjects undergoing US evaluation should not take NSAIDs for the last 48 hours prior to the US assessment. (See Section 5.2.3.2 Prohibited Therapy).

The ultrasound evaluation will comprise a comprehensive assessment of joints, entheses and tendons.

For the joint evaluation, the following 23 pairs of joints will be scanned:

- Metacarpophalangeal (MCP) joints 1 to 5,
- Proximal interphalangeal (PIP) joints 1 to 5,
- Distal interphalangeal (DIP) joints 2 to 5,

- Metatarsophalangeal (MTP) joints 1 to 5,
- Wrist, elbow, knee, ankle (tibiotalar).

The US assessment of synovitis will consist of an evaluation of hypoechoic synovial hyperplasia (SH) using Grayscale (or B mode) and synovial vascularization using Power Doppler (PDUS). The pre-specified set of 23 paired joints will be scanned in longitudinal and transverse scan from the dorsal aspect with the joint in a neutral position, except for the knee, which will also be examined in a flexed position (30°).

The presence of synovitis (i.e., SH and Power Doppler) will be scored according to the OMERACT-EULAR PDUS composite semi-quantitative scale (0 to 3).[53]

For the entheses evaluation, the following 5 pairs of entheses will be scanned:

1. Common extensor tendon insertion at the lateral humeral epicondyle,
2. Quadriceps tendon insertion at the superior pole of the patella,
3. Patellar tendon proximal insertion at the inferior pole of the patella,
4. Patellar tendon distal insertion at the tibia tuberosity,
5. Achilles tendon insertion at the calcaneus; plantar aponeuroses insertion at the calcaneus.

Each evaluated enthesis will be scored in terms of inflammatory (i.e., presence of Doppler signal within 2 mm from the cortical bony insertion and hypoechogenicity of the tendon insertion with or without increase of its thickness) and structural lesions (i.e., cortical abnormalities erosions and enthesophytes, and calcifications) according to the OMERACT enthesitis composite semi quantitative scale (0 to 3).[55]

Finally, the presence of tenosynovitis will be also recorded. The following 28 bilateral tendons will be assessed for Grayscale and Doppler tenosynovitis:

- Extensor compartments at the wrist (from 1-6),

- 2nd-5th finger flexor tendons,
- Tibialis posterior, flexor hallux longus, flexor digitorum common and peroneal tendons.

Evaluation and scoring will be performed according to the OMERACT definition and scoring system.[56]

Note: All the specified 46 joints and 10 entheses should be evaluated at every visit indicated in Appendix C. Only affected tendons will be assessed after Day 1 (Baseline). Standardized evaluation scans and examples of synovitis, enthesitis and tenosynovitis grading for each site examined will be available in an Atlas.

Details of US evaluation are presented in Appendix J.

Dispense Study Drug, Dosing and Compliance

Adalimumab and MTX

Study medication(s), dosing instructions and a dosing diary will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Appendix C. Investigators will be provided with additional MTX product information from the manufacturer. The first dose of study drug(s) will be administered after all other Baseline (Day 1) procedures are completed.

MTX will be provided for either oral or subcutaneous (sc) administration as requested by the Investigator. ADA and sc MTX 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.

Subjects or a designated family member or friend will be trained to administer study medication(s), 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(s) in the subject's home or in the clinic during the weeks the subjects are not in the office for scheduled study visits.

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

On those days that a study visit takes place, study medication is to be administered after all clinical assessments including questionnaires, ultrasound evaluation (if applicable) and vital sign determination.

Adalimumab should be administered sc at approximately the same time of the day eow or ew, as per study protocol (with the exception of office visits). At all office visits, subjects should be observed after study drug administration until judged clinically stable by the study personnel. Study drug should be administered after all clinical assessments including questionnaires and vital sign determination. 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. (See Section 6.1.7 for toxicity management).

MTX should be administered orally or sc at approximately the same time of the day ew. During the study subjects should continue with their regular MTX administration schedule prior to the study enrolment. If MTX is not routinely taken on the day of the study visit, the MTX will be dispensed to the subject and the subject will take the medication home and administer it at their regular schedule. There is no relation between the adalimumab and MTX administration schedule defined per this study protocol, but generally adalimumab and MTX are not recommended to be administered on the same day. See Section 5.5.1 Treatments Administered for additional information on MTX administration and dose escalation of MTX.

For subjects who deviate from the dosing schedule, every effort should be made to bring the subject back to the study Part 1 or 2 dosing schedule as soon as possible.

Subjects will maintain a dosing diary for all study drug administered outside of the study visit (i.e., at home) to capture dosing dates and times. The subject must be instructed to return study drug and diaries at each clinic visit for the purpose of compliance assessment and drug accountability as detailed in Section 5.5.7. At visits specified in Appendix C, the site personnel will review and retain a copy of the dosing diary, returned study drug kits, and empty study drug packaging to verify compliance. Additionally, any discernible departure from the protocol regarding study drug administration will be documented appropriately.

Randomization and Assignment of Subject Numbers

Subjects will be eligible for randomization if they continue to meet all of the selection criteria at Baseline and are willing to continue in the study.

Serum Adalimumab Concentrations

Samples will be obtained for serum adalimumab concentrations at the designated study visits as indicated in Appendix C and described in more detail under Section 5.3.2 only for subjects receiving adalimumab.

Anti-Adalimumab Antibodies (AAA)

Samples will be obtained for AAA at the designated study visits as indicated in Appendix C and described in more detail under Section 5.3.2 only for subjects receiving adalimumab.

Optional Samples for Exploratory Research and Validation Studies

Subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research/validation studies. The procedure for

obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

Exploratory research can help to improve our understanding of how individuals respond to drugs and our ability to predict which subjects would benefit from receiving specific therapies. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor PsA by assessing associations between disease characteristics, outcomes data and biomarkers of interests.

Validation studies, including those related to the development of potential in-vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

AbbVie (or people or companies working with AbbVie) will store the exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on adalimumab (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. Instructions for the preparation and shipment of the samples will be provided in a laboratory manual.

The following optional samples will be collected at the visits indicated in Appendix C.

- A single whole blood sample for pharmacogenetic analysis will be collected at Day 1 or any subsequent visit (if not obtained on Day 1)
- Whole blood for epigenetic analysis
- Whole blood for transcriptomic
- Serum and Plasma Samples for systemic analyses, including but not limited to proteomic and metabolomic

5.3.2 Drug Concentration Measurements

Blood samples for the pharmacokinetic (PK) measurement of serum ADA levels and anti-ADA antibody (AAA) concentrations will be taken at the designated visits, as specified in Appendix C only for subjects receiving adalimumab.

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 6 mL evacuated serum collection tubes without gel separator. Sufficient blood will be collected to provide approximately 2.4 mL serum for the adalimumab and AAA assays. 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).

5.3.2.1 Handling/Processing of Samples

The blood samples for adalimumab and AAA will be handled/processed as outlined below.

5.3.2.1.1 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 four aliquots, all 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 Split 1, PK Split 2, AAA Split 1, AAA Split 2). 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.

5.3.2.2 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.

5.3.2.3 Measurement Methods

Serum concentrations of adalimumab and AAA will be determined using validated ligand binding methods under the supervision of the Drug Analysis Department at AbbVie. Any additional analytes may be analyzed using non-validated methods. The residual serum volume of the samples may be used for future exploratory assay development and validation.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The proportion of subjects in MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew as compared with subjects on MTX alone escalated to 20- 25 mg or highest tolerable dose ew.

Minimal Disease Activity (MDA)

MDA in PsA is defined as fulfilling at least 5 of the 7 following criteria:[57,58]

- TJC ≤ 1 (out of TJC68 assessed in this study)

- SJC ≤ 1 (out of SJC66 assessed in this study)
- PASI ≤ 1 or BSA ≤ 3
- Patient's assessment of pain VAS ≤ 15
- Patient's global assessment of disease activity (PtGA) VAS ≤ 20
- HAQ-DI score ≤ 0.5
- Tender entheseal points ≤ 1 (out of 8 assessed in this study)

5.3.3.2 Secondary Variables

- The following outcomes after 16 Weeks of treatment with adalimumab 40 mg eow plus MTX 15 mg ew compared with MTX alone escalated to 20-25 mg or highest tolerable dose ew:
  - Change in PASDAS from baseline
  - Change in DAPSA score from baseline
  - Change in PsAID score from baseline
  - Proportion of subjects achieving ACR 20/50/70 response
  - Change in DAS28-CRP score from baseline
  - Proportion of subjects achieving PASI 75/90/100 response among subjects with BSA ≥ 3%
  - Change in HAQ-DI score from baseline
  - Changes in total SF-36 score, PCS and MCS from baseline
  - Change in DLQI score from baseline
  - Change in Leeds Enthesitis Index (LEI) from baseline
  - Change in tender dactylitic digit count from baseline
- The proportion of subjects in MDA at Week 32 on each of the four different treatment regimens (Arms 1-4) in Part 2 of the study.

Psoriatic Arthritis Disease Activity Score (PASDAS)

PASDAS is a weighted disease activity measure developed specifically for PsA. It includes PhGA, PtGA, SF-36 PCS, SJC, TJC, Leeds enthesitis count, tender dactylitic count and CRP.

PASDAS score is calculated by the following equation:[59]

$$\begin{aligned}\text{PASDAS} = (((&0.18\sqrt{\text{Physician global VAS}})\\ &+ (0.159\sqrt{\text{Patient global VAS}})\\ &- (0.253 \times \sqrt{\text{SF36-PCS}})\\ &+ (0.101 \times \text{LN}(\text{Swollen joint count} + 1))\\ &+ (0.048 \times \text{LN}(\text{Tender joint count} + 1))\\ &+ (0.23 \times \text{LN}(\text{Leeds Enthesitis Count} + 1))\\ &+ (0.37\,\text{LN}(\text{tender dactylitis count} + 1))\\ &+ (0.102 \times \text{LN}(\text{CRP} + 1)) + 2) * 1.5\end{aligned}$$

Disease Activity in Psoriatic Arthritis (DAPSA)

DAPSA is a PsA disease activity measure, calculated by summing SJC66 + TJC68 + Patient's assessment of pain + PtGA + CRP.[60-62]

American College of Rheumatology Criteria (ACR)

The ACR is a standard criteria originally developed to measure the effectiveness of various arthritis medications or treatments in clinical trials for RA, but is also widely used in PsA. The ACR measures improvement in TJC or SJC, and improvement in at least 3 of the following 5 parameters: Patient's assessment of pain, PtGA, PhGA, physical function (HAQ-DI) and acute phase reactant (CRP). ACR 20/50/70 response is achieved if ≥ 20%/≥ 50%/≥ 70% improvement in TJC or SJC as well as a ≥ 20%/≥ 50%/≥ 70% improvement in ≥ 3 of the other 5 parameters.[63]

Due to the specific of PsA (skin activity included in PtGA), ACR responses will be calculated both using PtGA and Patient's global assessment of arthritis in this study.

Disease Activity Score-28 (DAS28)

DAS28 is a weighted measure of disease activity originally developed for RA, but is also used in PsA clinical trials. DAS-28 includes TJC, SJC, PtGA and acute phase reactant (CRP in this study) and is calculated by the following equation:[64,65]

$$DAS28\text{-}CRP = 0.56 \times \sqrt{TJ} + 0.28 \times \sqrt{SJ} + 0.36 \times \ln(CRP^{*} + 1) + 0.014 \times PtGA + 0.96$$

* CRP unit in the DAS28-CRP equation is expressed as mg/L.

Due to the specific of PsA (skin activity included in PtGA), DAS28-CRP will be calculated both using PtGA and Patient's global assessment of arthritis in this study.

Psoriasis Area and Severity Index (PASI) 75/90/100

PASI 75/90/100 denotes ≥ 75%/≥ 90%/100% improvement in PASI score.[43,44]

5.3.3.3 Exploratory Variables

Clinical Effectiveness Variables

Clinical effectiveness outcomes listed under the secondary variables at Week 32 on the 4 different treatment regimens (Arms 1-4) in Part 2 of the study.

Ultrasound Variables

- The change in Global OMERACT-EULAR synovitis score (GLOESS) from baseline to Week 16 in subjects who had adalimumab introduced in combination with MTX compared with those who had MTX escalated to 20-25 mg ew or highest tolerable dose.
- The change in OMERACT enthesitis score from baseline to Week 16 in subjects who had adalimumab introduced in combination with MTX compared with those who had MTX escalated to 20-25 mg ew or highest tolerable dose.
- The change in Global OMERACT-EULAR synovitis score (GLOESS) from Week 16-32 in the 4 arms of Part 2 of the study.

- The change in OMERACT enthesitis score from Week 16-32 in the 4 arms of Part 2 of the study.

5.3.4 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.

5.3.5 Pharmacokinetic and Immunogenicity Variables

For subjects receiving adalimumab, blood samples will be collected for determination of adalimumab serum concentrations and the presence of anti-ADA antibodies (AAA) as specified in Appendix C.

5.3.6 Exploratory Research Variables and Validation Studies

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to: nucleic acids, proteins, lipids or metabolites.

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of PsA or related conditions and/or adalimumab or drugs of similar classes. The results from these analyses are exploratory in nature and may not be included with the study report.

The samples may also be used to develop new therapies, research methods or technologies. In addition, samples from this study may be banked for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

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 if any of the following occur:

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie TA MD.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Joint surgery
- The subject becomes pregnant while on study medication.
- Subject has known dysplasia of the gastrointestinal tract or 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 non-compliant with TB prophylaxis.
- The subject develops tuberculosis, or any other significant or opportunistic infections.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial in consultation with the AbbVie TA MD.

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

A final phone call will be made to the subject approximately 70 days (± 7 day window) after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs (as described in Section 5.1.2.2). The information will be recorded on the appropriate eCRF page.

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

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

Subjects who discontinue the study prematurely will not be replaced.

5.4.2 Discontinuation of Entire Study

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

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

5.5 Treatments

5.5.1 Treatments Administered

5.5.1.1 Adalimumab

Adalimumab will be administered in this study open-label and at the standard dosing regimen 40 mg sc eow except in one arm of Part 2 as described below.

- Subjects randomized to Arm 1/Part 1 or assigned to Arms 1 and 4 of Part 2 at Week 16 (as described in Section 5.1 and Table 2), will receive adalimumab 40 mg eow. Starting at the Baseline (Day 1) visit, subjects who are eligible for randomization will receive the first dose of study drug: adalimumab 40 mg/0.8 mL.
- Subjects assigned to Arm 2/Part 2 (as described in Section 5.1 and Table 2), will receive adalimumab 40 mg ew beginning at the Week 16 visit.
- Subjects entering the rescue arm at or after Week 24 will have adalimumab introduced or escalated at the Investigator's discretion. For the recommended rescue treatment regimens see Section 5.1 Overall Study Design and Plan: Description.

5.5.1.2 Methotrexate

MTX will be administered open-label either orally as tablets or subcutaneously by pre-filled pens (sc) as outlined below.

- Subjects randomized to Arm 1/Part 1 will continue at the stable dose of MTX 15 mg ew (as described in Section 5.1 and Table 3).
- Subjects randomized to Arm 2/Part 1 will increase MTX dose to 20-25 mg or highest tolerable dose ew as described below (see also Section 5.1 and Table 3).

- Subjects assigned to Arm 1/Part 2 will discontinue MTX at Week 16 (Section 5.1 and Table 3). MTX should be discontinued immediately and completely at the Week 16 Visit (subjects will not taper-off MTX).
- Subjects assigned to Arm 2/Part 2 will continue at the stable dose of MTX 15 mg ew after the Week 16 visit (see also Section 5.1 and Table 3).
- Subjects assigned to Arm 3/Part 2 will continue MTX at 20-25 mg or highest tolerable dose ew after the Week 16 Visit (as described in Section 5.1 and Table 3).
- Subjects assigned to Arm 4/Part 2 will continue MTX at 20-25 mg or highest tolerable dose ew after the Week 16 Visit (as described in Section 5.1 and Table 3).
- Subjects entering the rescue arm at or after Week 24 will have MTX introduced or escalated at the Investigator's discretion. For the recommended rescue treatment regimens see Section 5.1 Overall Study Design and Plan: Description.

During the study subjects should remain on their regular MTX administration schedule as prior to the study and MTX should be taken on the same day and approximately the same time of day ew.

The escalation of MTX dose in Arm 2/Part 1 should be in the increments of 5 mg every two weeks until the MTX dose of 20-25 mg ew is reached.[27,66,67] The dose escalation begins on Day 1, starting with MTX 20 mg ew as the first MTX dose at or after Day 1, as applicable according to the MTX administration schedule prior to study enrolment. The dose of MTX should only be escalated providing there are no clinical and/or laboratory signs of MTX intolerance or toxicity.

In the case of clinical and/or laboratory signs of MTX intolerance/toxicity, MTX dose may be de-escalated by 5 mg, including during the MTX escalation period.[67,68] The subject may stay on the highest tolerable MTX dose which is lower than 20-25 mg ew if MTX intolerance/toxicity occurred, see Section 6.1.7 for additional information. MTX dose should not exceed 25 mg ew in this study.

Change in the route of MTX administration (between oral and sc) is allowed at any time as deemed necessary by the Investigator. Switching from oral to sc administration may improve MTX bioavailability and/or decrease MTX intolerance/toxicity, particularly at MTX doses ≥ 20 mg ew.[69]

The tolerability of oral MTX at doses ≥ 20 mg ew may also be improved by dividing the total dose of MTX into two administrations on the same day, but not exceeding the total daily dose of MTX to be taken in the week.

All subjects receiving MTX in this study are recommended to be on folic or folinic acid supplementation with the dose and regimen chosen at the Investigator's discretion (see Section 5.2.3.1 Prior and Concomitant Therapy).

There is no required timely relationship between MTX and adalimumab administration per this protocol, but in general MTX and adalimumab are not advised to be administered on the same day.

5.5.2 Identity of Investigational Product

Information about the adalimumab formulation to be used in this study is presented in Table 2.

Table 2. Identity of Investigational Product – Adalimumab

Investigational Product	Adalimumab Solution for Injection, 50 mg/mL (40 mg/0.8 mL) Pre-Filled Syringe
Dosage Form	Solution for injection in pre-filled syringe
Formulation	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
Strength (mg)	40 mg/0.8 mL
Mode of Administration	Subcutaneous injection
Manufacturer	AbbVie Deutschland GmbH & Co. KG

Mode of administration for adalimumab is subcutaneous injection.

Adalimumab, solution for injection, 50 mg/mL (40 mg/0.8 mL) do not require reconstitution before use.

Information about the MTX formulation to be used in this study is presented in Table 3.

Table 3. Identity of Investigational Product – MTX

Investigational Product	MTX Tablets	MTX Pre-Filled Pen
Dosage Form	Tablet	Solution for injection in pre-filled pen
Strength (mg)	5mg	15 mg/0.30 ml 20 mg/0.40 ml 25 mg/0.50 ml
Mode of Administration	Orally	Subcutaneous injection
Manufacturer	Teva/Hexal	Medac

5.5.2.1 Packaging and Labeling

Adalimumab, solution for injection, 50 mg/mL (40 mg/0.8 mL) will be packaged in cartons containing 2 pre-filled syringes. Each pre-filled syringe and carton will be labeled as required per country requirements. Labels must remain affixed to the syringe and carton. Each kit label will contain a unique kit number. The type and amount of kits dispensed will be managed by the IRT.

Subjects will receive blister cartons or bottles containing MTX tablets. Each blister carton or bottle will contain 30 tablets of MTX 5 mg. Each drug will be labeled as per country requirements. Labels must remain affixed to the supplies. Each kit label will contain a unique kit number. The type and amount of kits dispensed will be managed by the IRT. MTX for injection will be provided as 15 mg/0.30 ml, 20 mg/0.40 ml and 25 mg/0.50 ml solution for injection in pre-filled pens, packaged in cartons. Each pen and carton will be labeled as required per local requirements. Each label must remain affixed to the supplies. Each kit label will contain a unique kit number. The type and amount of kits dispensed will be managed by the IRT.

5.5.2.2 Storage and Disposition of Study Drugs

Adalimumab 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 and temperature excursions 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.

MTX tablets must be stored at 15° to 25°C, protected from light.

MTX prefilled pens for injection must be stored at 15° to 25°C, protected from light and must not be frozen.

All clinical supplies must be stored and locked in a secure place and stored under the conditions specified on the label 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 centrally randomized using IRT. Before the study is initiated, IRT directions will be provided to each site.

All subjects will be assigned a unique identification number by the IRT at the Screening visit. Subjects who meet the inclusion and exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be centrally randomized in a 1:1 ratio to adalimumab + MTX or MTX alone on Day 1 (Baseline). Using IRT, subjects will be first stratified by the duration of MTX treatment at 15 mg ew into two strata: ≤ 3 months and > 3 months. Then within each stratum, the IRT will assign a randomization number that will encode the subject's

treatment group assignment according to the randomization schedule generated by the Statistics Department at AbbVie.

After the assessment of MDA at Week 16, subjects will be assigned to one of the four treatment arms of Part 2 (Arms 1-4) as described in Section 5.1 for an additional 16 weeks using IRT. Additionally, IRT will be used to dispense study medication if a subject changes the mode of MTX administration (i.e., oral to sc or sc to oral) and if applicable decreases the dose of MTX (e.g., change from 25 mg sc to 20 mg sc or change from 20 mg sc to 15 mg sc). The sites will register changes in dose and mode of administration into IRT.

IRT will provide the appropriate medication kit number(s) to dispense to each subject. Study drug will be administered at the study visits as summarized in Appendix C. Returned study medication should not be re-dispensed to any subject.

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 study medication (adalimumab or MTX) on their regularly scheduled dosing date, they should take the forgotten medication 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 for adalimumab and MTX separately on the Subject-Dosing Diary.

Doses of adalimumab or MTX not administered (e.g., not taken before next dose is scheduled), should be recorded as not taken in the source and Subject-Dosing Diary. The remaining extra study drug should be returned to the study site full. For subjects who

deviate from the dosing schedule, every effort should be made to bring the subject back to their Part 1 or 2 dosing schedule as soon as possible.

5.5.5 Blinding

This study is open-label study. Blinding is not applicable.

5.5.6 Treatment Compliance

The Investigator or his/her designated representatives will dispense study drugs 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 Subject-Dosing Diary for adalimumab and MTX to record all dosing dates and times. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of medication and it should be documented in the subjects' source. If the subject does not return the dosing diary, 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 and documented in the source 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 and in the correct amounts. For adalimumab, in the US/Puerto Rico adequate temperature is cool to the touch, for non-US sites, temperature recording devices (temptales) are provided in the shipments. 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 IRT will be used to document investigational product accountability including but not limited to date received, the lot number, Kit number(s), date dispensed, subject number and identification of person dispensing the drug.

All empty IP boxes (tablets, pen, prefilled syringes) and the status of each bottle, number of tablets remaining in each one returned, will be inventoried by the site. Each subject will be given their own sharps disposal container to store used adalimumab pre-filled syringes and/or methotrexate pre-filled pens, if necessary. Empty IP boxes, empty bottles, any unused study drug and Sharps containers should be returned by the subject at each visit for accountability and compliance purposes and new containers issued as necessary. Site staff will complete study medication accountability in IRT, using source documents, subject dosing diaries, empty IP boxes, bottles and by visually inspecting the syringes and/or pens in the Sharps container whenever possible. Used Sharps containers should never be opened. The site monitor will verify drug accountability either at the site or during remote monitoring and will complete the reconciliation in IRT. The site staff will document that the used pre-filled syringes and/or pens have been destroyed, using appropriate biohazard precautions, when appropriate. All study drug unit doses must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. For IRT accountability/reconciliation, lost status does not apply to empty boxes and bottles not returned. If a subject returns to a site for a visit with proof of taking all doses (verbal and/or dosing diary) the IP is documented as used. In all cases, comments should be documented in source and IRT (e.g., 'subject lost to follow-up, no medication returned; study drug verified, subject did not return empty boxes').

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is an open-label, randomized, controlled, parallel-group, multi-country study in subjects with PsA consisting of 2 parts: Part 1 is designed to compare the achievement of MDA between subjects randomized to either adalimumab introduced in combination with MTX or MTX alone escalated to the highest recommended or tolerable dose; Part 2 is to compare the maintenance or achievement of MDA between four different treatment regimens using adalimumab and/or MTX, with subject allocation based on the initial randomized treatment and achievement of MDA in Part 1.

An open label design was chosen to be able to allow for the subcutaneous and not solely oral MTX use. Although oral MTX is the usual way of using MTX in PsA, some patients may be switched to parenteral MTX in the case of gastrointestinal intolerance or insufficient effectiveness in clinical practice. This is a pragmatic study, aiming to reflect and inform clinical practice.

Subjects eligible for the study are required to have prior MTX therapy at 15 mg ew for at least 4 weeks. The MTX dose of 15 mg ew was selected as the currently recommended starting MTX dose.[66,67] Additionally, 15 mg ew or slightly higher is also the average MTX dose seen in clinical practice.[15,20-23] Four weeks is considered to be the minimum period to establish therapeutic effect of MTX.[38] The treatment regimens investigated in Part 2 of the study are used in clinical practice but lack scientific evidence.

MDA was selected as the primary effectiveness variable for the following reasons: it is a composite disease activity measure encompassing all crucial domains of PsA, including patient perspective, and has been well validated in PsA; corresponds to the status of remission or low disease activity; has been shown to be associated with long-term patient benefits in terms of less radiographic progression and improvements in PROs, has been recommended as the treatment target in PsA; was shown to be able to discriminate between active treatment and placebo as well as different treatment regimens (T2T approach and standard of care).[11,25-27,34,53,55,70-72]

5.6.2 Appropriateness of Measurements

All effectiveness measurements in this study are standard and validated.[41] All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

This is a pragmatic study designed to assess the effectiveness of adalimumab introduced in combination with MTX compared with MTX alone escalated to the highest recommended[11,27] or tolerable dose.

The study will enroll adult male and female subjects with active PsA (defined as not in MDA and having ≥ 3 tender and ≥ 3 swollen joints) despite treatment with MTX at 15 mg ew for at least 4 weeks who have not been receiving a prior biologic for PsA. At enrollment, the study subjects will have been treated for a relatively short period of time with 15 mg MTX ew, and will require treatment modification/adjustment due to inadequate disease control. It is estimated that by not being in MDA and having ≥ 3 tender and ≥ 3 swollen joints, the subjects will have a sufficient level of PsA disease activity to compare the effectiveness of adalimumab in combination with stable dose of MTX and escalated MTX. The subjects need to be bDMARD naive at enrolment in order to be able to assess the effectiveness of bDMARD introduction.

5.6.4 Selection of Doses in the Study

Adalimumab will be administered in this study at the approved dosing regimen for PsA (i.e., 40 mg sc eow).[36,37] The only exception will be subjects not achieving MDA on the approved adalimumab dosing in combination with MTX, who will be required to escalate adalimumab to 40 mg sc ew in combination with MTX (Arm 2/Part 2). Adalimumab 40 mg ew has been used in ACR20 non-responders in the open-label extension of the ADEPT trial up to Week 144 with no increased risk of adverse events.[30,31] Adalimumab has been approved in the EU for weekly dosing in psoriasis patients with inadequate response after 16 weeks of treatment.[36] Adalimumab may be used with or without concomitant methotrexate in PsA according to the label.[36,37]

The highest recommended MTX dose of 20-25 mg ew in this study is in line with the international recommendations for the management of PsA.[11] This dose, along with the MTX dose escalation scheme required in this study, has been studied in subjects with PsA before,[18,27] though with a different research objective. The dosing of MTX is also in line with the MTX prescribing information for PsA.[38]

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 compounds and
- Device components (pre-filled syringe and pen).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events (AEs), 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 another 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.

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

Assessment of adverse event relationship to the study medications(s) will be made with respect to adalimumab and MTX. 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.
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, another cause of event must be provided by the investigator for the serious adverse event.

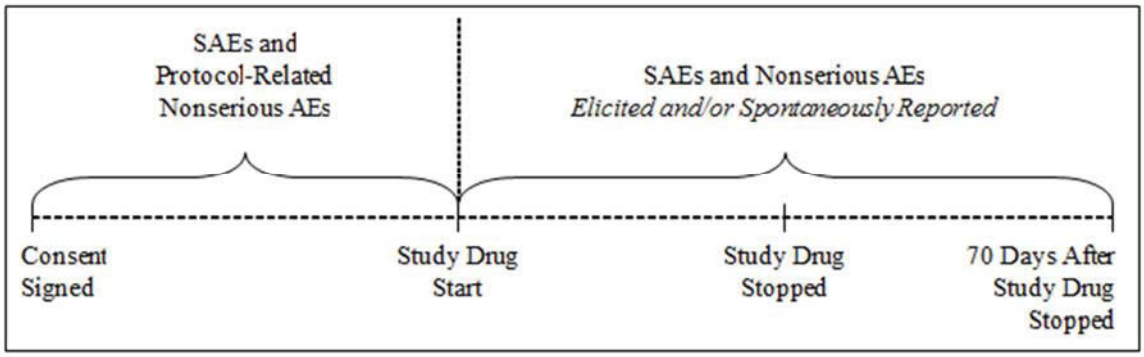
6.1.4 Adverse Event Collection Period

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 will be contacted 70 days (± 7 day window) following study drug discontinuation for an assessment of any new or ongoing AEs. All SAEs and all ongoing adverse events reported during the 70-day follow-up phone call must be captured in the clinical database.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in subjects 30 years of age and younger, whether related to study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the event by entering the serious adverse event or non-serious event of malignancy in subjects 30 years of age and younger data into the RAVE® electronic data capture (EDC) system. Serious adverse events and non-serious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® system or if RAVE® is not operable should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Immunology Safety Team at:

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

Office: [redacted]
Email:

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

Primary Therapeutic Area Medical Director:

[redacted], MD
[redacted]
Global Medical Affairs Rheumatology
AbbVie
[redacted]
26525 North Riverwoods Blvd
Mettawa, IL 60045

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

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

Phone: [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries for adalimumab will be the most current version of SmPC (prescribing information). The reference document used for SUSAR reporting in the EU countries for MTX will be the MTX prescribing information provided to the investigator.

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). Pregnancies in study subjects and their partners will be collected from the date of the first dose through 180 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

Adalimumab

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.

Methotrexate

The definition of MTX intolerance and/or toxicity is based on MTX intolerance and toxicity as described in the MTX prescribing information provided to the investigator. An event of intolerance or toxicity is to be recorded as AE. The decision for treatment adjustment is at the investigator's discretion.

MTX will be escalated by 5.0 mg every 2 weeks. If MTX intolerance/toxicity is suspected, MTX dose reduction by 5 mg, including during the escalation period, may be performed. Any subject who cannot tolerate the highest recommended dose specified in the protocol (20-25 mg ew) due to toxicity or intolerance, is permitted to continue on the highest tolerable dose.

Temporary MTX discontinuation followed by re-introduction/re-escalation of MTX is allowed if the issue resolves within 4 weeks. The TA MD must be consulted if the Investigator would like to temporarily discontinue MTX more than one time.

If the investigator would like to decrease the MTX dose for any reasons other than MTX intolerance/toxicity, the AbbVie TA MD must be contacted first.

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 subject 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 AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be

accommodated within 30 days, the site will need to provide justification and an estimated date of return.

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Contacts:

Primary Contact:

[redacted]

1 North Waukegan Road
North Chicago, IL 60064
USA

Office: [redacted]
Fax:

Alternate Contact:

[redacted]

94528 Rungis Cedex
France

Office: [redacted]
Fax:

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

8.1.1 Analysis Population

The primary and secondary efficacy endpoints will be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication. Subjects in the ITT population will be analyzed according to the treatment group they were randomized to. In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary efficacy endpoint may be conducted on the per protocol population if deemed necessary. The Per Protocol population consists of all ITT subjects who entered the randomized period of the study and did not meet any major protocol violation during the Part 1 of the study.

The safety population consists of all subjects who received at least one dose of study medication.

8.1.2 Statistical and Analytical Plan

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 tests will be conducted at $\alpha = 0.05$ level (2-sided). Descriptive statistics will be provided including but not limited to the number of observations, mean, standard deviation, median, minimum and maximum for continuous endpoints; and counts and percentages for binary endpoints.

A Week 16 database lock is planned when all randomized subjects have completed Week 16 (Part 1) of the study. The Week 16 study results (through Week 16) will be based on this database lock. Statistical comparisons for the primary and secondary efficacy endpoints will be performed at Week 16 between the Part 1 treatment groups. No multiplicity adjustment will be performed for the statistical tests since there is only one primary endpoint.

Data from the subsequent period (Part 2) will be reported at the completion of the study by Part 2 treatment groups.

The last available pre-treatment values recorded on or before Day 1 (the first dose of Part 1) will be considered as the Baseline value for efficacy analysis. All subsequent study visits will be determined in reference to the baseline.

To account for missing data for the binary efficacy endpoints, a non-responder imputation approach (NRI) will be used, i.e., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder. For continuous endpoints, the Mixed-effects Model Repeated Measures (MMRM) analysis based on all observed data will be used.

The rescued patients' last observation on or before the rescued visit will be included in the analysis of Part 2 treatments. The efficacy and safety after the rescue will be summarized separately for the rescued patients.

8.1.3 Analysis of Demographic Data and Baseline Disease Characteristics

Demographic and Baseline characteristics will be summarized by treatment groups. The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables; Binary endpoints will be summarized via counts and percentages.

Duration of study treatment will be summarized. Medical History will be summarized by body system and diagnosis. Prior and concomitant medication will be summarized using the World Health Organization (WHO) Drug Dictionary.

8.1.4 Statistical Analysis of Efficacy

8.1.4.1 Primary Efficacy Variable

The primary endpoint is the proportion of subjects achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew as compared with subjects on MTX alone escalated to 20-25 mg or highest tolerable dose ew.

The null hypothesis is that there is no difference in response rates between the adalimumab + MTX and MTX groups; the alternative hypothesis is that the response rates between the treatment groups are different. The response rates will be tested using a Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor of the duration of prior (to screening) use of MTX at 15 mg ew. The stratification factor is defined as the duration of prior MTX 15 mg ew use of ≤ 3 months or > 3 months.

Sensitivity analyses will be conducted using the same method described above using observed cases (OC).

8.1.4.2 Analyses of Secondary Efficacy Variables

A complete list of secondary efficacy endpoints is provided in Section 5.3.3.2. Binary secondary endpoints in Part 1 will be summarized using count and percentages and will be compared between treatment groups using CMH test adjusting for the stratification factor of the duration of prior use of MTX.

MDA at Week 32 is a Part 2 endpoint and it will be summarized by four treatment regimens. No statistical testing will be performed.

For the continuous secondary endpoints, the change from baseline at Week 16 will be analyzed using MMRM with treatment, stratification factor of prior MTX use, visit, and

treatment-by-visit interaction as fixed effects, subject as random effect and baseline value as a covariate. The MMRM analysis is based on all observed data. The LS mean, 95% CI and standard error for each randomized treatment group, the LS mean of the treatment difference and its associated 95% CI and p-value from the MMRM model will be presented.

8.1.4.3 Other Exploratory Analyses

Analysis for other efficacy endpoints referenced in (Section 5.3.3.3) will be performed using similar methods to those described in Section 8.1.4.2.

For ultrasound assessment in Part 1, baseline weight will also be included as additional covariate in MMRM.

8.1.5 Statistical Analyses of Safety

Safety analyses will be carried out using safety population, which includes all subjects that received at least one dose of study medication. Treatment-emergent 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, and up to within 70 days after the last dose of the study medication. All treatment emergent AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®). The number and percent of subjects experiencing AEs will be tabulated by system organ class and preferred term. In addition, a summary of AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, which lead to premature study discontinuation will be listed and described in detail. Adverse event of special interest (AESI) will also be tabulated.

Observed values of vital signs and laboratory variables at each visit will be summarized for all treated subjects, and change from baseline in selected lab variables will be compared between treatment groups using a one way ANOVA. The last evaluation prior

to the first dose of study drug will be used as Baseline for the analyses in Part 1. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) (Version 3) of Grade 3 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variable.

8.1.6 Subject Disposition and Study Drug Exposure

The number of subjects will be tabulated overall for the following categories: randomized, ITT population, completed (e.g., Part 1), and discontinued for each treatment group and for the total sample as appropriate. The reasons for discontinuation will also be summarized per CRF categories.

Treatment compliance will be summarized for adalimumab and MTX respectively for Part 1 and Part 2, as appropriate. Adalimumab 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%). MTX compliance will be calculated as the number of tablets/injections actually received divided by the number of tablets/injections expected during the participation in the study. Compliance will be summarized for the ITT population.

8.1.7 Pharmacokinetic and Immunogenicity Analyses

Adalimumab serum trough concentrations will be summarized by treatment arm at each time point using descriptive statistics including number of subjects, number of non-missing observations (nnmiss), 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. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F).

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

8.2 Determination of Sample Size

The study is powered to detect the difference in MDA response rates at Week 16 between adalimumab + MTX 15 mg and MTX escalated dose groups. Assuming an MDA response rate of 40% in the adalimumab + MTX group and 20% in the escalated MTX group, a total sample size of 240 subjects, 120 subjects per arm, will provide at least 90% statistical power to detect the difference between the two treatment groups with a significance level of 0.05, allowing approximately 10% dropout.

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.

Following local regulation, substantial amendments may also be reviewed and approved by the national competent authority.

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. 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.

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional exploratory research/validation studies. The

nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the optional exploratory research/validation studies, it will not impact their participation in the study.

In the event a subject withdraws consent to participate from the study, stored exploratory research/validation studies samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining exploratory research/validation studies samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

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.

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 exploratory research/validation studies that may be done using the samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management, hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from exploratory research/validation studies from this study may be used in scientific publications or presented at medical conventions. Exploratory research/validation studies data 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.

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 Medicines Evaluation Agency (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 SmPC or prescribing information for adalimumab and the product labeling for adalimumab and methotrexate.
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 open-label randomized controlled study **CO**mparing the effectiveness of ada**L**imumab i**NTRO**duction with methotrexate dose esca**L**ation in subjects with Psoriatic Arthritis (CONTROL)
Protocol Date:	03 June 2019

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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71. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res (Hoboken). 2010;62:965-9.

72. Kavanaugh A, van der Heijde D, Beutler A, et al. Patients with psoriatic arthritis who achieve minimal disease activity in response to golimumab therapy demonstrate less radiographic progression: results through 5 years of the

randomized, placebo-controlled, GO-REVEAL study. Arthritis Care Res (Hoboken). 2016;68(2):267-74.

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/competent authority reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Global Medical Affairs
		Global Medical Affairs
		Clinical Pharmacology & Pharmacometrics
		Statistics
		Bioanalysis
		Clinical Program Development
		Statistics

Appendix C. Study Activities

Activity	Screening[a]	Day 1 Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32/PD	70 Day F/U Visit/Call
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X[b]										
Confirm PsA diagnosis	X											
Medical/Surgical History	X	X[c]										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Exam[d]	X	X										
Vital Signs/Weight/Height[e]	X	X	X	X	X	X	X	X	X	X	X	
12 Lead ECG	X[f]											
Chest X-Ray	X[g]											
Central lab QuantiFERON-TB Gold teste (and/or local PPD skin test)	X[h]											
Hematology	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[i]	X	X	X	X	X	X	X	X	X	X	X	
CRP		X	X	X	X	X	X	X	X	X	X	
HIV[j]	X											
HBV and HCV Screening	X											
Urine Pregnancy Test		X	X	X	X	X	X	X	X	X	X	

Activity	Screening[a]	Day 1 Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32/PD	70 Day F/U Visit/Call
Serum Pregnancy Test[k]	X											
Blood samples for PK[l]		X		X	X	X	X	X	X	X	X	
Blood samples for AAA[l]		X		X	X	X	X	X	X	X	X	
66 – Swollen Joint Count (SJC66)	X	X	X	X	X	X	X	X	X	X	X	
68 – Tender Joint Count (TJC68)	X	X	X	X	X	X	X	X	X	X	X	
Physician's global assessment of disease activity (PhGA)		X	X	X	X	X	X	X	X	X	X	
PASI	X	X	X	X	X	X	X	X	X	X	X	
Body surface area (BSA)	X	X	X	X	X	X	X	X	X	X	X	
Leeds Enthesitis Index	X	X	X	X	X	X	X	X	X	X	X	
Tenderness at the plantar fascia	X	X	X	X	X	X	X	X	X	X	X	
Dactylitis		X	X	X	X	X	X	X	X	X	X	
Psoriatic Arthritis Impact of Disease (PsAID)		X	X	X	X	X	X	X	X	X	X	
Patient's assessment of pain	X	X	X	X	X	X	X	X	X	X	X	
Patient's global assessment of disease activity (PtGA)	X	X	X	X	X	X	X	X	X	X	X	
Patients' global assessment of arthritis	X	X	X	X	X	X	X	X	X	X	X	

Activity	Screening[a]	Day 1 Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32/PD	70 Day F/U Visit/Call
Health Assessment Questionnaire – Disability Index (HAQ-DI)	X	X	X	X	X	X	X	X	X	X	X	
Short Form-36 (SF 36)		X		X		X	X		X		X	
Self-Assessment of Psoriasis Symptoms (SAPS)		X	X	X	X	X	X	X	X	X	X	
Dermatology Life Quality Index (DLQI)		X		X		X	X		X		X	
Ultrasound (if applicable)[m]		X		X			X				X	
Randomization		X										
Dispense Study Drug(s)		X	X	X	X	X	X	X	X	X		
Dispense Dosing Instructions		X					X[n]					
Dispense Dosing Diary		X					X[n]					
Review and copy subject dosing diary, monitor compliance and perform drug Reconciliation			X	X	X	X	X	X	X	X	X	
Monitor Adverse Events	X[o]	X	X	X	X	X	X	X	X	X	X	X
Optional Exploratory Research: Pharmacogenetic samples[o]		X										
Optional Exploratory Research: Epigenetic samples[o]		X	X	X			X				X	

Activity	Screening[a]	Day 1 Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32/PD	70 Day F/U Visit/Call
Optional Exploratory Research: Transcriptomic samples[o]		X	X	X			X				X	
Optional Exploratory Research: Samples for proteomic and targeted protein investigations (Plasma)[p]		X	X	X			X				X	
Optional Exploratory Research: Samples for proteomic and targeted protein investigations (Serum)[p]		X	X	X			X				X	

PD = Premature discontinuation; F/U = Follow-Up

a. Perform within 30 days prior to study drug administration.

b. Before study drug administration, all inclusion and exclusion criteria should be re-confirmed based on assessments completed during the Screening period.

c. Update history.

d. A symptom directed physical exam should be performed when necessary and if needed for physician assessments/questionnaires.

e. Height will be measured at Screening only and weight will be measured at the Screening and Week 32/PD.

f. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required.

g. Chest x-ray not required at Screening if subject had a previous normal chest x-ray within 90 days of Screening.

h. Subjects treated with corticosteroids (equivalent to Prednisone 5 mg or above – with ongoing treatment or treatment within 1 month to TB screeening) must be screened with a QuantiFERON-TB Gold In-tube test or equivalent (central lab). Subjects NOT treated with corticosteroids can be screened with a PPD skin test (alternatively, also known as tuberculin skin test) locally or an Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) centrally.

i. Dipstick urinalysis will be completed by the central lab at all required visits. A microscopic analysis will be performed at Screening and in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

j. If required by country regulatory authorities or deemed warranted by the Investigator to confirm eligibility, subjects will be tested for HIV and documented that the test has been performed. This testing is to be done at a local laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

k. All females of childbearing potential will have a serum pregnancy test at Screening. In addition to the screening serum pregnancy test, 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.

l. PK and AAA samples will be collected only for subjects receiving adalimumab.

m. Ultrasound will be performed on all subjects at sites that participate in the US assessment.

n. Subjects assigned to Part 2, Arm 4, will be given an adalimumab dosing diary and instruction at Week 16.

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

p. Optional samples: Subject will sign additional consent forms; if the additional consent forms are not signed, no optional samples will be collected.

Appendix D. Class VI and Class VII Topical Corticosteroid Examples

Class	Generic Name or Local Equivalent	%
VI	Prednicarbate	0.05
	Triamcinolone acetonide	0.025
	Desonide	0.05
	Fluocinolone acetonide	0.01
	Triamcinolone acetonide	0.025
	Flumethasone pivalate	0.03
	Fluocinolone acetonide	0.01
	Desonide	0.05
	Triamcinolone acetonide	0.025
	Betamethasone valerate	0.01
VII	Betamethasone valerate	0.2
	Hydrocortisone acetate	1.0
	Hydrocortisone	1.0, 2.5
	Methylprednisolone	0.25
	Fluorometholone	0.025
	Hydrocortisone	1.0, 2.5

Appendix E. Tender Joint Count (TJC) and Swollen Joint Count (SJC) Assessment

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

Joint Evaluation

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

Appendix F. Dactylitis Assessment

Please indicate which DIGITS are **SWOLLEN ONLY** or **SWOLLEN & PAINFUL** with a tick.

Left Hand					
Digit	**5**	**4**	**3**	**2**	**Thumb**
Swollen only					
Swollen & painful					

Right Hand				
Thumb	**2**	**3**	**4**	**5**

Left Foot					
Digit	**5**	**4**	**3**	**2**	**Hallux**
Swollen only					
Swollen & painful					

Right Foot				
Hallux	**2**	**3**	**4**	**5**

Dactylitic count = Number of swollen digits (range 0-20).

Tender dactylitic count = Number of swollen and painful digits (range 0-20).

Appendix G. Enthesitis Assessment: Leeds Enthesitis Index and Tenderness at the Plantar Fascia

Leeds Enthesitis Index (LEI)

Please tick for each tender enthesis	Tender Right	Tender Left
Medial condyle femur	☐	☐
Lateral epicondyle humerus	☐	☐
Achilles tendon insertion	☐	☐

LEI = Number of tender entheses (0-6)

Tenderness at the Plantar Fascia

Please tick for tender enthesis	Tender Right	Tender Left
Insertion of plantar fascia to the calcaneus	☐	☐

Total number of enthesitis sites = LEI + number of tender plantar fascias (range 0-8).

Appendix H. Psoriasis Area and Severity Index (PASI)

Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration and desquamation using a 5-point scale:

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

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

- 1 = < 10%
- 2 = 10%-29%
- 3 = 30%-49%
- 4 = 50%-69%
- 5 = 70%-89%
- 6 = 90%-100%

Since the head, upper extremities, trunk and lower extremities correspond to approximately 10%, 20%, 30% and 40% of body surface area, respectively; the PASI score is calculated using the formula:

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

where *E, I, D,* and *A* denote erythema, induration, desquamation, and area, respectively, and *h, u, t,* and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest possible degree. Typically scores of 3 or less

represent mild disease, scores over 3 and up and including 15 represent moderate disease and scores over 15 are considered to be associated with severe disease.

Appendix I. Physician's Global Assessment of Disease Activity (PhGA)

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

Please mark the line below to indicate patient's current disease activity considering both musculoskeletal and skin disease activity.

0	100
Disease not active at all	Disease extremely active

Appendix J. Ultrasound Assessments and Scoring

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

PDUS evaluation will be performed at 46 joints, 10 entheses and 28 tendons/tendon synovial compartments (see also Ultrasound evaluation in Section 5.3.1.1 Study Procedures).

Joints Evaluation

Twenty-three (23) pairs of joints will be scanned at each time point:

- Metacarpophalangeal (MCP) joints 1 to 5,
- Proximal interphalangeal (PIP) joints 1 to 5,
- Distal interphalangeal (DIP) 2 to 5,
- Metatarsophalangeal (MTP) joints 1 to 5,
- Wrist, elbow, knee and ankle (tibiotalar).

The pre specified set of 23 paired joints will be scanned in longitudinal and transverse scan from the dorsal aspect with the joint in a neutral position, except for the knee, which will also be examined in a flexed position (30°).

The US assessment will consist of an evaluation of hypoechoic synovial hyperplasia (SH) using Grayscale (or B mode) and synovial vascularization using PDUS. The presence of synovitis (i.e., SH and Power Doppler signal) will be scored according to the OMERACT-EULAR PDUS composite semi-quantitative scale (0 to 3).[53]

Table. Ultrasound Scoring Systems of Synovitis at Joint and Patient Levels.[53]

Joint level (for individual joints)

A) Single components

Greyscale inflammatory (hypoechoic) synovial hyperplasia

- Grade 0: No hypoechoic synovial hyperplasia
- Grade 1: Minimal hypoechoic synovial hyperplasia (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones)
- Grade 2: Hypoechoic synovial hyperplasia bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis
- Grade 3: Hypoechoic synovial hyperplasia bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphysis

Power Doppler Signal

- Grade 0: No flow in the hypoechoic synovial hyperplasia
- Grade 1: Up to 3 single spots signals or up to 2 confluent spots or 1 confluent spot plus up to 2 single spots
- Grade 2: Vessel signals in less than half of the area of the synovium (< 50%)
- Grade 3: Vessel signals in more than half of the area of the synovium (> 50%)

B) Composite Score

OMERACT-EULAR composite PDUS synovitis score

- Grade 0 (normal joint): No greyscale-detected synovial hyperplasia and no PD signal
- Grade 1 (minimal synovitis): Grade 1 synovial hyperplasia and ≤ Grade 1 PD signal
- Grade 2 (moderate synovitis): Grade 2 synovial hyperplasia and ≤ Grade 2 PD signal; OR Grade 1 synovial hyperplasia and a Grade 2 PD signal
- Grade 3 (severe synovitis): Grade 3 synovial hyperplasia and ≤ Grade 3 PD signal; OR Grade 1 or 2 synovial hyperplasia and a Grade 3 PD signal

Patient Level

Global OMERACT-EULAR Synovitis Score (GLOESS)

- Sum of composite PDUS scores for all joints assessed

Entheses Evaluation

The following 5 entheses will be evaluated bilaterally:

1. Common extensor tendon insertion at the lateral humeral epicondyle,
2. Quadriceps tendon insertion at the superior pole of the patella,
3. Patellar tendon proximal insertion at the inferior pole of the patella,
4. Patellar tendon distal insertion at the tibia tuberosity,
5. Achilles tendon insertion and plantar aponeuroses insertion at the calcaneus.

For the enthesis evaluation, US will be initially performed in B mode to detect morphologic abnormalities, and subsequently with power Doppler to detect abnormal vascularization at bony insertion. For each enthesis the following elementary lesions will be recorded within 2 mm from the cortical bone, according to the OMERACT definition of enthesitis:[55]

- Presence of Doppler signal,
- Hypoechogenicity of the tendon insertion,
- Thickening of tendon insertion,
- Erosions,
- Enthesophytes,
- Calcifications.

Except for the presence of Doppler signal, each elementary lesion will be scored binary as present or absent. The presence of Doppler signal will be scored semiquantitative as 0 (absent) to 3 (severe), according to the following semi-quantitative grade:

- 0 = absent
- 1 = maximum 3 Doppler spots,
- 2 = more than 3 and less than 50% of the enthesis area
- 3 = more than 50% of the enthesis area

Tenosynovitis Evaluation

The following 14 tendon compartments will be assessed bilaterally for the presence of GS and Doppler tenosynovitis:

- Extensor compartments at the wrist (1 to 6),
- 2nd-5th finger flexor tendons,
- Tibialis posterior, flexor hallux longus, flexor digitorum common and peroneal tendons.

Presence and grading of tenosynovitis will be defined and performed according to the OMERACT definition and scoring system.[56]

Note: Standardized evaluation scans and examples of synovitis, enthesitis and tenosynovitis grading for each site examined will be available in an Atlas.

Technical Requirements:

Different models of ultrasound machines are allowed as long as B-mode (Greyscale) and high quality Doppler modules are available. It is recommended to use high-end machines as per the training Atlas which will be provided. B-mode and Doppler machine settings will be optimized before the study and standardized for the whole study.

US Assessment Conditions:

The US assessments must be performed by an expert in musculoskeletal US with verifiable training and/or certification and at least 3 years of experience. Ideally, the ultrasonographer should have prior experience in multicenter study(ies); otherwise training will be provided. The Ultrasonographer must be independent of the clinical Investigator and should be blinded for subject characteristics and treatment arm; he/she should be the same person throughout the study, and a back-up with the same qualifications should be appointed. The clinical assessor will be blinded to the US scoring.

The US assessment should be performed in a darkened room with temperature kept stable. Subjects are recommended to stop NSAIDs intake, if present, within the prior 48 hours of each US evaluation.

Further details about probe position will be provided in the US Atlas.

Appendix K. 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 [redacted] North Chicago, IL 60064 USA	For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany
	[redacted], MD, PhD [redacted] Global Medical Affairs Rheumatology AbbVie Dolenjska cesta 242c Ljubljana SI-1000 Slovenia	Phone: Mobile: Fax: [redacted]

Has been changed to read:

Sponsor:	For Non-EU Countries: AbbVie 1 North Waukegan Road [redacted] North Chicago, IL 60064 USA	For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie) Knollstrasse 50 67061 Ludwigshafen Germany
Sponsor/Emergency Medical Contact:	[redacted], MD [redacted] Global Medical Affairs Rheumatology AbbVie [redacted] 26525 North Riverwoods Blvd Mettawa, IL 60045 Phone: Mobile: [redacted] **Sponsor contact for all non-emergency issues:** [redacted], PhD [redacted] Immunology Pipeline Global Medical Affairs AbbVie [redacted] 26525 North Riverwoods Blvd Mettawa, IL 60045 Phone: Mobile: [redacted] Email: [redacted]	

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-496
Name of Study Drug: Adalimumab	**Phase of Development:** 4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 09 March 2018
Protocol Title: A Phase 4 open-label randomized controlled study **CO**mparing the effectiveness of adalimumab i**NTRO**duction and methotrexate dose esca**L**ation in subjects with Psoriatic Arthritis (CONTROL)	

Objectives:

Primary Objective

The primary objective is to compare the effectiveness based on the achievement of minimal disease activity (MDA) at Week 16 between subjects who had adalimumab introduced and those that had methotrexate (MTX) escalated to the highest recommended dose of 20-25 mg every week (ew) or highest tolerable dose up to 25 mg ew after inadequate disease control on the initial MTX therapy.

Secondary Objectives

- To compare the effectiveness at Week 16 between subjects who had adalimumab introduced and those that had MTX escalated to the highest recommended dose of 20-25 mg ew or highest tolerable up to 25 mg ew based on the following clinical, functional and quality of life measures:
  - Psoriatic Arthritis Disease Activity Score (PASDAS)
  - Disease Activity in Psoriatic Arthritis (DAPSA) score
  - Psoriatic Arthritis Impact of Disease (PsAID) score
  - American College of Rheumatology criteria (ACR)
  - Disease Activity Score 28 (DAS28)
  - Psoriasis Area and Severity Index (PASI)
  - Health Assessment Questionnaire Disability Index (HAQ-DI)
  - Short Form Health Survey 36 (SF-36) scores: total, physical component summary (PCS) and mental component summary (MCS)
  - Dermatology Life Quality Index (DLQI)
  - Leeds Enthesitis Index (LEI)
  - Tender dactylitic digit count
- To evaluate the achievement of MDA at Week 32 on each of the four different treatment regimens involving adalimumab and/or MTX in Part 2 of the study.

The study also has the following **Exploratory Objectives:**

- To evaluate the effectiveness at Week 32 based on the clinical, physical function and quality of life measures described under the secondary objectives on each of the four different treatment regimens involving adalimumab and/or MTX in the second part of the study.
- To evaluate ultrasound detected synovitis and enthesitis at joint and enthesis level, and treatment effect on each of the study treatment regimens.

Objectives (Continued):

Exploratory Objectives (Continued)

- To assess the pharmacokinetic and immunogenicity of adalimumab with and without concomitant MTX.
- To investigate various biomarkers and their associations with treatment responses and outcomes.

Investigators: Multi-center

Study Sites: Approximately 60 sites

Study Population: Approximately 240 adult subjects with active PsA (defined as not in MDA and having at least 3 tender and 3 swollen joints) despite having been treated with the first course of MTX at the dose of 15 mg ew for ≥ 4 weeks and biologic naive who meet all the inclusion and none of the exclusion criteria are planned to be enrolled in the study.

Number of Subjects to be Enrolled: 240 subjects in total, 120 subjects per randomized arm.

Methodology: This interventional Phase 4 open-label, randomized, controlled, parallel-group, multicenter study will be conducted in two (2) parts, each of 16-week duration.

Part 1 (Day 1-Week 16) is designed to compare the achievement of MDA on adalimumab introduced in combination with MTX versus MTX alone escalated to the highest recommended dose of 20-25 mg ew or highest tolerable dose up to 25 mg ew, whatever feasible, in PsA subjects inadequately controlled after the initial course of MTX at 15 mg ew. Part 1 will be open-label, randomized, controlled, parallel group.

Part 2 (Week 16-32) is to evaluate the effectiveness of four (4) different treatment regimens consisting of adalimumab and/or MTX in maintaining or attaining MDA, as applicable. Part 2 will be open-label, parallel group. Subjects will be assigned into the four treatment arms based on their MDA status at Week 16 and initial randomized treatment. Starting at Week 24, there will be rescue treatment option based on not achieving MDA and investigator's judgment.

Following a maximum 30-day screening period, subjects meeting the selection criteria will be randomized in a 1:1 ratio to either of the two (2) arms and treated for 16 weeks in Part 1:

- Arm 1/Part 1: Adalimumab 40 mg eow in combination with MTX 15 mg ew (adalimumab 40 mg eow + MTX 15 mg ew),
- Arm 2/Part 1: MTX escalated to 20-25 mg or highest tolerable dose ew (MTX 20-25 mg or highest tolerable dose ew)*
  - * MTX will be escalated by increments of 5.0 mg every 2 weeks, starting at 20 mg ew as the first MTX dose on or after Day 1, depending on the subject's MTX administration schedule prior to the study. In the case of suspected MTX intolerance or toxicity, the MTX dose may be de-escalated by 5 mg and the subject may stay on the highest tolerable MTX dose below 20-25 mg ew as described per the protocol. MTX dose should not exceed 25 mg ew in this study.

Methodology (Continued):

After the assessment of MDA at Week 16 (primary endpoint), subjects will be assigned to one of the 4 treatment arms based on the achievement of MDA and initial randomized treatment, and treated for additional 16 weeks in Part 2 as follows:

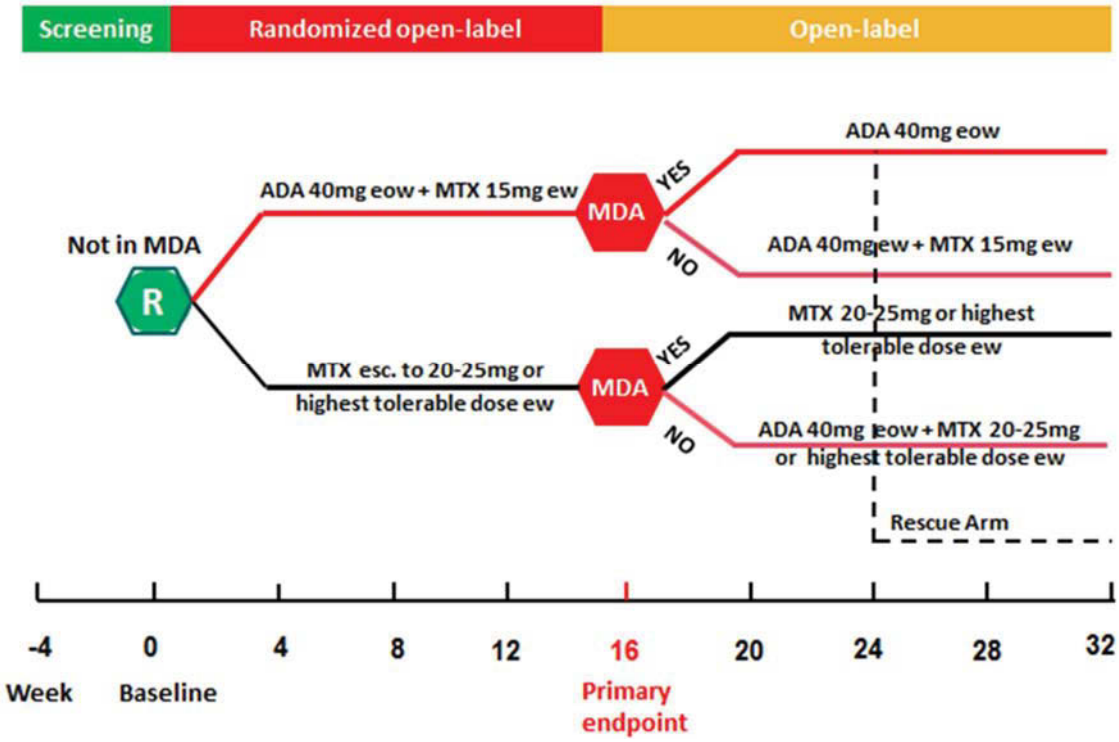
- Arm 1/Part 2: Subjects achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have MTX completely withdrawn at Week 16 and continue receiving adalimumab as monotherapy (adalimumab 40 mg eow),
- Arm 2/Part 2: Subjects not achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have adalimumab escalated to 40 mg ew in combination with MTX 15 mg ew (adalimumab 40 mg ew plus MTX 15 mg ew),
- Arm 3/Part 2: Subjects achieving MDA at Week 16 on MTX escalated to 20-25 mg or highest tolerable dose ew, will continue with the same MTX dose (MTX 20-25 mg or highest tolerable dose ew),
- Arm 4/Part 2: Subjects not achieving MDA at Week 16 on MTX escalated to 20-25 mg or highest tolerable dose ew, will receive adalimumab 40 mg eow in combination with MTX 20-25 mg or highest tolerable dose ew (adalimumab 40 mg eow plus MTX 20-25 mg or highest tolerable dose ew).

Subjects in Arms 1-4 of Part 2 of the study will have the option of being rescued, starting at Week 24 and based on the subject not achieving MDA and the Investigator's judgment. The selection of the rescue treatment regimen will be at the discretion of the Investigator, but should involve adalimumab and/or MTX and should not involve prohibited medications per the protocol. The recommended rescue treatment regimens are as follows:

- Subjects not achieving MDA on adalimumab 40 mg eow (Arm 1) have MTX 15 mg ew added,
- Subjects not achieving MDA on adalimumab 40 mg ew + MTX 15 mg ew (Arm 2) have MTX escalated to 20-25 mg ew,
- Subjects not achieving MDA on MTX 20-25 mg or highest tolerable dose ew (Arm 3) have adalimumab 40 mg eow added,
- Subjects not achieving MDA on adalimumab 40 mg eow + MTX 20-25 mg or highest tolerable dose ew (Arm 4) have adalimumab escalated to 40 mg ew.

Methodology (Continued):

A schematic of the study design is shown in the following figure:



Both adalimumab and MTX will be provided as study drugs.

MTX will be provided as a study drug for either oral or subcutaneous (sc) administration. The route of MTX administration can be selected at the discretion of the Investigator and may be exchanged between oral and sc at any time during the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, ≥ 18 years of age at Screening
2. PsA diagnosis established at least 4 weeks prior to the date of the Screening visit and confirmed by C1ASsification of Psoriatic Arthritis (CASPAR) criteria at the Screening visit
3. Not in MDA at the time of screening, defined as not meeting at least 5 of the following 7 criteria:
   - Tender joint count (TJC) ≤ 1 out of 68 assessed
   - Swollen joint count (SJC) ≤ 1 out of 66 assessed
   - PASI ≤ 1 or Body Surface Area (BSA) ≤ 3
   - Patient's assessment of pain visual analogue scale (VAS) ≤ 15

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

Main Inclusion (Continued):

- Patient's global assessment of disease activity (PtGA) VAS ≤ 20
- HAQ-DI score ≤ 0.5
- Tender entheseal points ≤ 1 out of 8 assessed

4. Has active arthritis defined as fulfilling both the below criteria at screening and baseline visits:
   - ≥ 3 tender joints (out of 68 assessed)
   - ≥ 3 swollen joints (out of 66 assessed)
5. Treated with MTX 15 mg ew for PsA defined as:
   - Oral or subcutaneous (sc) administration of MTX for at least 4 weeks prior to screening,
   - Change of the MTX administration route (oral or sc) is permitted in this time period if the administered dose of MTX 15 mg ew is not changed,
   - This is the first course of MTX the subject has been receiving for the treatment of PsA,
   - Subject has not received a dosage of MTX higher than 15 mg ew prior to the screening visit
   - Subject could have been receiving MTX doses lower than 15 mg ew before reaching the stable dose of MTX 15 mg ew defined above,
   - If the subject had been on MTX 15 mg ew for ≥ 12 weeks, temporary MTX discontinuation or dose decrease below 15 mg ew for up to 4 weeks is allowed.
6. If subject is receiving concomitant oral corticosteroids, prednisone or equivalent must be ≤ 10 mg/day and the dose must be stable for at least 1 week prior to the baseline visit.
7. If subject is receiving nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX) 2 selective inhibitors, paracetamol (up to the maximum recommended dose in the local country label), the dose must be stable for at least 1 week prior to the Baseline Visit
8. If subject is receiving other csDMARDs in addition to MTX (i.e., sulfasalazine), the dose must be stable for at least 4 weeks prior to the baseline visit. If csDMARDs are discontinued before study enrollment, the discontinuation must occur at least 4 weeks prior to the baseline Visit.
   - Leflunomide should be discontinued at least 4 weeks prior to the baseline visit.

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Has contraindication(s) to adalimumab therapy and/or known hypersensitivity to adalimumab or its excipients (refer to SmPC or prescribing information)
2. Has history of MTX intolerance/toxicity
3. Has medical condition(s) precluding MTX dose increase above 15 mg ew
4. Has had prior exposure to any tumor necrosis factor (TNF) inhibitor, other mechanism of action biologic DMARD (bDMARD) or any systemic biologic agent in general

Investigational Product:	Adalimumab, solution for injection 50 mg/mL (40 mg/0.8 mL) pre-filled syringe (PFS)
Doses:	40 mg administered eow or ew
Mode of Administration:	Subcutaneous (sc) injection
Reference Therapy:	Methotrexate Tablets: 5 mg Methotrexate Pre-filled PEN: 15 mg/0.30 ml 20 mg/0.40 ml 25 mg/0.50 ml
Dose:	Methotrexate ew
Mode of Administration:	Orally or sc
Duration of Treatment: Up to 32 weeks	

Criteria for Evaluation:

Effectiveness:

Primary Endpoint

The proportion of subjects in MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew as compared with subjects on MTX alone escalated to 20-25 mg or highest tolerable dose ew.

Secondary Endpoints

- The following outcomes after 16 Weeks of treatment with adalimumab 40 mg eow plus MTX 15 mg ew compared with MTX alone escalated to 20-25 mg or highest tolerable dose ew:
  - Change in PASDAS from baseline
  - Change in DAPSA score from baseline
  - Change in PsAID score from baseline
  - Proportion of subjects achieving ACR 20/50/70 response
  - Change in DAS28-CRP score from baseline
  - Proportion of subjects achieving PASI 75/90/100 response among subjects with BSA ≥ 3%
  - Change in HAQ-DI score from baseline
  - Changes in total SF-36 score, PCS and MCS from baseline
  - Change in DLQI score from baseline
  - Change in Leeds Enthesitis Index (LEI) from baseline
  - Change in tender dactylitic digit count from baseline
- The proportion of subjects in MDA at Week 32 on each of the four different treatment regimens (Arms 1-4) in Part 2 of the study.

Exploratory Variables:

Clinical Effectiveness Variables

Clinical effectiveness outcomes listed under the secondary endpoints at Week 32 on the 4 different treatment regimens (Arms 1-4) in Part 2 of the study.

Criteria for Evaluation (Continued):

Ultrasound Variables

- The change in Global OMERACT-EULAR synovitis score (GLOESS) from baseline to Week 16 in subjects who had adalimumab introduced compared with those who had MTX escalated to 20-25 mg or highest tolerable dose ew.
- The change in OMERACT enthesitis score from baseline to Week 16 in subjects who had adalimumab introduced compared with those who had MTX escalated to 20-25 mg or highest tolerable dose ew.
- The change in Global OMERACT-EULAR synovitis score (GLOESS) from Week 16-32 in the 4 arms of Part 2 of the study.
- The change in OMERACT enthesitis score from Week 16-32 in the 4 arms of Part 2 of the study.

Pharmacokinetic and Immunogenicity: For subjects receiving adalimumab, blood samples will be collected for determination of adalimumab serum concentrations and the presence of anti-adalimumab antibodies (AAA).

Exploratory Research Variables and Validation Studies (Optional): Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to: nucleic acids, proteins, lipids or metabolites.

Safety: 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.

Statistical Methods:

Effectiveness: The primary and secondary effectiveness variables will be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication. Unless otherwise stated, all statistical tests will be conducted at $\alpha = 0.05$ level (2-sided). Descriptive statistics will be provided including but not limited to the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables; and counts and percentages for discrete variables. Statistical comparisons for the primary and secondary effectiveness endpoints will be performed at Week 16 between the Part 1 treatment groups. No multiplicity adjustment will be performed for the statistical tests. An interim database lock is planned when all randomized subjects have completed Week 16 (Part 1) of the study. To account for missing data for the discrete effectiveness endpoints, a non-responder imputation approach (NRI) will be used, i.e., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder. The last observation carried forward (LOCF) rule will be used to impute missing continuous effectiveness endpoints. In addition, an analysis using all observed data adjusting for baseline values will be performed as a sensitivity analysis for the effectiveness endpoints, using mixed-effects model repeated measures (MMRM) for continuous variables and logistic random-effect model for binary endpoints. The rescued patients' last observation on or before the rescued visit will be included in the analysis of Part 2 treatments. The efficacy and safety after the rescue will be summarized separately for the rescued patients.

Statistical Methods (Continued):

Effectiveness (Continued):

The response rates for the primary endpoint will be tested using a Cochran-Mantel-Haenszel (CMH) test adjusting for strata (duration of baseline use of MTX). Stratum is defined as the duration of baseline MTX use at 15 mg ew ≤ 3 months or > 3 months. Secondary analyses of the primary endpoint will be conducted using all observed cases up to Week 16. Logistic regression model with stratum, treatment, visit, and treatment-by-visit interaction as fixed effects, subject as random intercept and baseline as covariate will be employed.

Discrete secondary variables will be summarized using count and percentages and will be compared between treatment groups using CMH test. Continuous secondary variables will be summarized by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum). Change from Baseline in the continuous variables will be analyzed using analysis of covariance (ANCOVA) with treatment as fixed effect and baseline value as a covariate for LOCF imputation. MMRM will be used for observed cases with stratum, treatment, visit, and treatment-by-visit interaction as fixed effects, subject as random effect and baseline value as covariate.

Pharmacokinetic and Immunogenicity: Adalimumab serum trough concentrations will be summarized by treatment arm at each time point using descriptive statistics including number of subjects, number of non-missing observations (nnmiss), 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. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F).

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

Ultrasound: Analysis will be performed using similar methods to those described for the primary and secondary effectiveness variables. Baseline weight will also be included as additional covariate in ANCOVA and MMRM.

Safety: Safety analyses will be carried out using safety population, which includes all subjects that received at least one dose of study medication. Treatment-emergent, and pre- and post-treatment 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, and up to within 70 days after the last dose of the study medication. All treatment emergent AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®). The number and percent of subjects experiencing AEs will be tabulated by system organ class and preferred term. In addition, a summary of AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, which lead to premature study discontinuation will be listed and described in detail. Adverse events of special interest (AESI) will also be tabulated.

Statistical Methods (Continued):

Safety:

Mean change in vital signs and laboratory variables at each visit as compared to baseline will be summarized for all treated subjects, and compared between treatment groups using a one way ANOVA. The last evaluation prior to the first dose of study drug will be used as Baseline 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 Baseline according to the normal range will also be provided for laboratory variable.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M14-496
Name of Study Drug: Adalimumab	**Phase of Development:** 4
Name of Active Ingredient: Adalimumab	**Date of Protocol Synopsis:** 03 June 2019
Protocol Title: A Phase 4 open-label randomized controlled study **CO**mparing the effectiveness of adalimumab i**NTRO**duction and methotrexate dose esca**L**ation in subjects with Psoriatic Arthritis (CONTROL)	

Objectives:

Primary Objective

The primary objective is to compare the effectiveness based on the achievement of minimal disease activity (MDA) at Week 16 between subjects who had adalimumab introduced and those that had methotrexate (MTX) escalated to the highest recommended dose of 20 – 25 mg every week (ew) or highest tolerable dose up to 25 mg ew after inadequate disease control on the initial MTX therapy.

Secondary Objectives

- To compare the effectiveness at Week 16 between subjects who had adalimumab introduced and those that had MTX escalated to the highest recommended dose of 20 – 25 mg ew or highest tolerable up to 25 mg ew based on the following clinical, functional and quality of life measures:
  - Psoriatic Arthritis Disease Activity Score (PASDAS)
  - Disease Activity in Psoriatic Arthritis (DAPSA) score
  - Psoriatic Arthritis Impact of Disease (PsAID) score
  - American College of Rheumatology criteria (ACR)
  - Disease Activity Score 28 (DAS28)
  - Psoriasis Area and Severity Index (PASI)
  - Health Assessment Questionnaire Disability Index (HAQ-DI)
  - Short Form Health Survey 36 (SF-36) scores: total, physical component summary (PCS) and mental component summary (MCS)
  - Dermatology Life Quality Index (DLQI)
  - Leeds Enthesitis Index (LEI)
  - Tender dactylitic digit count
- To evaluate the achievement of MDA at Week 32 on each of the four different treatment regimens involving adalimumab and/or MTX in Part 2 of the study.

The study also has the following **Exploratory Objectives:**

- To evaluate the effectiveness at Week 32 based on the clinical, physical function and quality of life measures described under the secondary objectives on each of the four different treatment regimens involving adalimumab and/or MTX in the second part of the study.
- To evaluate ultrasound detected synovitis and enthesitis at joint and enthesis level, and treatment effect on each of the study treatment regimens.

Objectives (Continued):

Exploratory Objectives (Continued)

- To assess the pharmacokinetic and immunogenicity of adalimumab with and without concomitant MTX.
- To investigate various biomarkers and their associations with treatment responses and outcomes.

Investigators: Multi-center

Study Sites: Approximately 60 sites

Study Population: Approximately 240 adult subjects with active PsA (defined as not in MDA and having at least 3 tender and 3 swollen joints) despite having been treated with the first course of MTX at the dose of 15 mg ew for ≥ 4 weeks and biologic naive who meet all the inclusion and none of the exclusion criteria are planned to be enrolled in the study.

Number of Subjects to be Enrolled: 240 subjects in total, 120 subjects per randomized arm.

Methodology: This interventional Phase 4 open-label, randomized, controlled, parallel-group, multicenter study will be conducted in two (2) parts, each of 16-week duration.

Part 1 (Day 1-Week 16) is designed to compare the achievement of MDA on adalimumab introduced in combination with MTX versus MTX alone escalated to the highest recommended dose of 20 – 25 mg ew or highest tolerable dose up to 25 mg ew, whatever feasible, in PsA subjects inadequately controlled after the initial course of MTX at 15 mg ew. Part 1 will be open-label, randomized, controlled, parallel group.

Part 2 (Week 16-32) is to evaluate the effectiveness of four (4) different treatment regimens consisting of adalimumab and/or MTX in maintaining or attaining MDA, as applicable. Part 2 will be open-label, parallel group. Subjects will be assigned into the four treatment arms based on their MDA status at Week 16 and initial randomized treatment. Starting at Week 24, there will be rescue treatment option based on not achieving MDA and investigator's judgment.

Following a maximum 30-day screening period, subjects meeting the selection criteria will be randomized in a 1:1 ratio to either of the two (2) arms and treated for 16 weeks in Part 1:

- Arm 1/Part 1: Adalimumab 40 mg eow in combination with MTX 15 mg ew (adalimumab 40 mg eow + MTX 15 mg ew),
- Arm 2/Part 1: MTX escalated to 20 – 25 mg or highest tolerable dose ew (MTX 20 – 25 mg or highest tolerable dose ew)*
  - * MTX will be escalated by increments of 5.0 mg every 2 weeks, starting at 20 mg ew as the first MTX dose on or after Day 1, depending on the subject's MTX administration schedule prior to the study. In the case of suspected MTX intolerance or toxicity, the MTX dose may be de-escalated by 5 mg and the subject may stay on the highest tolerable MTX dose below 20 – 25 mg ew as described per the protocol. MTX dose should not exceed 25 mg ew in this study.

Methodology (Continued):

After the assessment of MDA at Week 16 (primary endpoint), subjects will be assigned to one of the 4 treatment arms based on the achievement of MDA and initial randomized treatment, and treated for additional 16 weeks in Part 2 as follows:

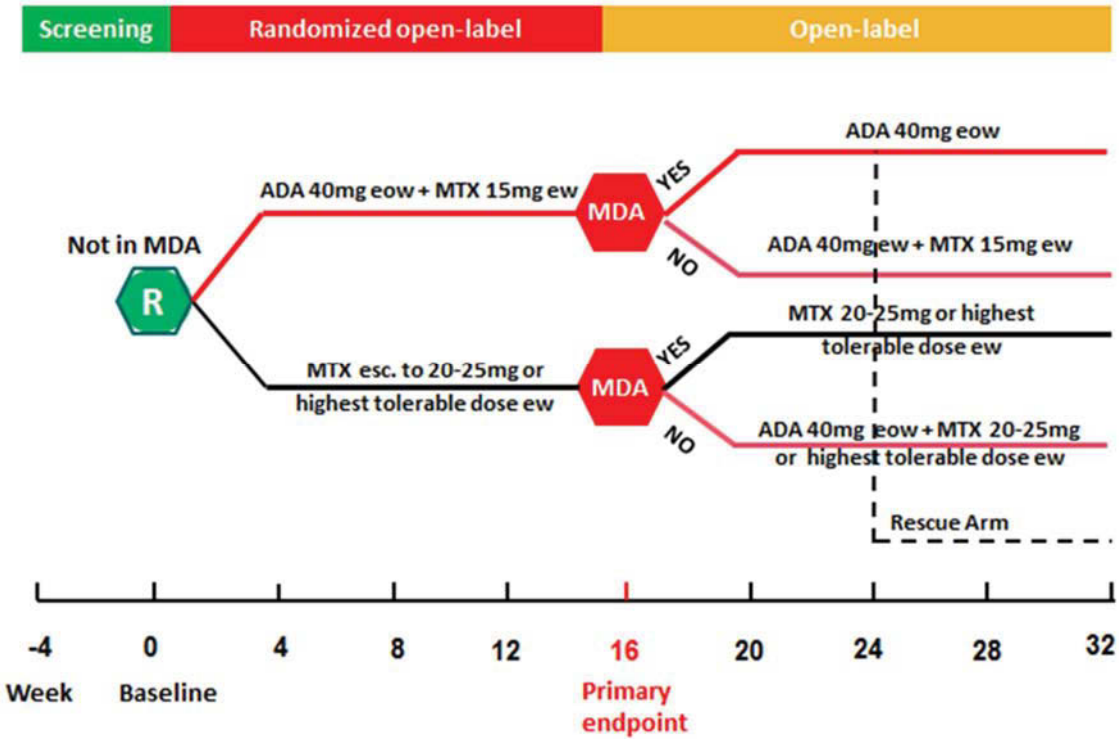
- Arm 1/Part 2: Subjects achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have MTX completely withdrawn at Week 16 and continue receiving adalimumab as monotherapy (adalimumab 40 mg eow),
- Arm 2/Part 2: Subjects not achieving MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew, will have adalimumab escalated to 40 mg ew in combination with MTX 15 mg ew (adalimumab 40 mg ew plus MTX 15 mg ew),
- Arm 3/Part 2: Subjects achieving MDA at Week 16 on MTX escalated to 20 – 25 mg or highest tolerable dose ew, will continue with the same MTX dose (MTX 20 – 25 mg or highest tolerable dose ew),
- Arm 4/Part 2: Subjects not achieving MDA at Week 16 on MTX escalated to 20 – 25 mg or highest tolerable dose ew, will receive adalimumab 40 mg eow in combination with MTX 20 – 25 mg or highest tolerable dose ew (adalimumab 40 mg eow plus MTX 20 – 25 mg or highest tolerable dose ew).

Subjects in Arms 1-4 of Part 2 of the study will have the option of being rescued, starting at Week 24 and based on the subject not achieving MDA and the Investigator's judgment. The selection of the rescue treatment regimen will be at the discretion of the Investigator, but should involve adalimumab and/or MTX and should not involve prohibited medications per the protocol. The recommended rescue treatment regimens are as follows:

- Subjects not achieving MDA on adalimumab 40 mg eow (Arm 1) have MTX 15 mg ew added,
- Subjects not achieving MDA on adalimumab 40 mg ew + MTX 15 mg ew (Arm 2) have MTX escalated to 20 – 25 mg ew,
- Subjects not achieving MDA on MTX 20 – 25 mg or highest tolerable dose ew (Arm 3) have adalimumab 40 mg eow added,
- Subjects not achieving MDA on adalimumab 40 mg eow + MTX 20 – 25 mg or highest tolerable dose ew (Arm 4) have adalimumab escalated to 40 mg ew.

Methodology (Continued):

A schematic of the study design is shown in the following figure:



Both adalimumab and MTX will be provided as study drugs.

MTX will be provided as a study drug for either oral or subcutaneous (sc) administration. The route of MTX administration can be selected at the discretion of the Investigator and may be exchanged between oral and sc at any time during the study.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, ≥ 18 years of age at Screening
2. PsA diagnosis established at least 4 weeks prior to the date of the Screening visit and confirmed by C1ASsification of Psoriatic Arthritis (CASPAR) criteria at the Screening visit
3. Not in MDA at the time of screening, defined as not meeting at least 5 of the following 7 criteria:
   - Tender joint count (TJC) ≤ 1 out of 68 assessed
   - Swollen joint count (SJC) ≤ 1 out of 66 assessed
   - PASI ≤ 1 or Body Surface Area (BSA) ≤ 3
   - Patient's assessment of pain visual analogue scale (VAS) ≤ 15

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

Main Inclusion (Continued):

- Patient's global assessment of disease activity (PtGA) VAS ≤ 20
- HAQ-DI score ≤ 0.5
- Tender entheseal points ≤ 1 out of 8 assessed

4. Has active arthritis defined as fulfilling both the below criteria at screening and baseline visits:
   - ≥ 3 tender joints (out of 68 assessed)
   - ≥ 3 swollen joints (out of 66 assessed)
5. Treated with MTX 15 mg ew for PsA defined as:
   - Oral or subcutaneous (sc) administration of MTX for at least 4 weeks prior to screening,
   - Change of the MTX administration route (oral or sc) is permitted in this time period if the administered dose of MTX 15 mg ew is not changed,
   - This is the first course of MTX the subject has been receiving for the treatment of PsA,
   - Subject has not received a dosage of MTX higher than 15 mg ew prior to the screening visit
   - Subject could have been receiving MTX doses lower than 15 mg ew before reaching the stable dose of MTX 15 mg ew defined above,
   - If the subject had been on MTX 15 mg ew for ≥ 12 weeks, temporary MTX discontinuation or dose decrease below 15 mg ew for up to 4 weeks is allowed.
6. If subject is receiving concomitant oral corticosteroids, prednisone or equivalent must be ≤ 10 mg/day and the dose must be stable for at least 1 week prior to the baseline visit.
7. If subject is receiving nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase (COX) 2 selective inhibitors, paracetamol (up to the maximum recommended dose in the local country label), the dose must be stable for at least 1 week prior to the Baseline Visit
8. If subject is receiving other csDMARDs in addition to MTX (i.e., sulfasalazine), the dose must be stable for at least 4 weeks prior to the baseline visit. If csDMARDs are discontinued before study enrollment, the discontinuation must occur at least 4 weeks prior to the baseline Visit.
   - Leflunomide should be discontinued at least 4 weeks prior to the baseline visit.

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Has contraindication(s) to adalimumab therapy and/or known hypersensitivity to adalimumab or its excipients (refer to SmPC or prescribing information)
2. Has history of MTX intolerance/toxicity
3. Has medical condition(s) precluding MTX dose increase above 15 mg ew
4. Has had prior exposure to any tumor necrosis factor (TNF) inhibitor, other mechanism of action biologic DMARD (bDMARD) or any systemic biologic agent in general

Investigational Product:	Adalimumab, solution for injection 50 mg/mL (40 mg/0.8 mL) pre-filled syringe (PFS)
Doses:	40 mg administered eow or ew
Mode of Administration:	Subcutaneous (sc) injection
Reference Therapy:	Methotrexate Tablets: 5 mg Methotrexate Pre-filled PEN: 15 mg/0.30 ml 20 mg/0.40 ml 25 mg/0.50 ml
Dose:	Methotrexate ew
Mode of Administration:	Orally or sc
Duration of Treatment: Up to 32 weeks	

Criteria for Evaluation:

Effectiveness:

Primary Endpoint

The proportion of subjects in MDA at Week 16 on adalimumab 40 mg eow plus MTX 15 mg ew as compared with subjects on MTX alone escalated to 20-25 mg or highest tolerable dose ew.

Secondary Endpoints

- The following outcomes after 16 Weeks of treatment with adalimumab 40 mg eow plus MTX 15 mg ew compared with MTX alone escalated to 20-25 mg or highest tolerable dose ew:
  - Change in PASDAS from baseline
  - Change in DAPSA score from baseline
  - Change in PsAID score from baseline
  - Proportion of subjects achieving ACR 20/50/70 response
  - Change in DAS28-CRP score from baseline
  - Proportion of subjects achieving PASI 75/90/100 response among subjects with BSA ≥ 3%
  - Change in HAQ-DI score from baseline
  - Changes in total SF-36 score, PCS and MCS from baseline
  - Change in DLQI score from baseline
  - Change in Leeds Enthesitis Index (LEI) from baseline
  - Change in tender dactylitic digit count from baseline
- The proportion of subjects in MDA at Week 32 on each of the four different treatment regimens (Arms 1 – 4) in Part 2 of the study.

Exploratory Endpoints:

Clinical Effectiveness

Clinical effectiveness outcomes listed under the secondary endpoints will be analyzed at Week 32 as exploratory endpoints on the 4 different treatment regimens (Arms 1-4) in Part 2 of the study.

Criteria for Evaluation (Continued):

Ultrasound

- The change in Global OMERACT-EULAR synovitis score (GLOESS) from baseline to Week 16 in subjects who had adalimumab introduced compared with those who had MTX escalated to 20 – 25 mg or highest tolerable dose ew.
- The change in OMERACT enthesitis score from baseline to Week 16 in subjects who had adalimumab introduced compared with those who had MTX escalated to 20 – 25 mg or highest tolerable dose ew.
- The change in Global OMERACT-EULAR synovitis score (GLOESS) from Week 16 – 32 in the 4 arms of Part 2 of the study.
- The change in OMERACT enthesitis score from Week 16 – 32 in the 4 arms of Part 2 of the study.

Pharmacokinetic and Immunogenicity: For subjects receiving adalimumab, blood samples will be collected for determination of adalimumab serum concentrations and the presence of anti-adalimumab antibodies (AAA).

Exploratory Research Variables and Validation Studies (Optional): Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to: nucleic acids, proteins, lipids or metabolites.

Safety: 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.

Statistical Methods:

Effectiveness: The primary and secondary efficacy endpoints will be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication. Unless otherwise stated, all statistical tests will be conducted at $\alpha = 0.05$ level (2-sided). A Week 16 database lock is planned when all randomized subjects have completed Week 16 (Part 1) of the study and statistical comparisons for the primary and secondary efficacy endpoints will be performed at Week 16 between the Part 1 treatment groups. No multiplicity adjustment will be performed for the statistical testing.

To account for missing data for the binary effectiveness endpoints, a non-responder imputation approach (NRI) will be used, e.g., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder. For continuous endpoints, the Mixed-effects Model Repeated Measures (MMRM) analysis based on all observed data will be used.

Statistical Methods (Continued):

Effectiveness (Continued):

The response rates for the primary endpoint will be compared between the treatment groups using a Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor, the duration of prior MTX use of ≤ 3 months or > 3 months. The primary analysis will be based on NRI and the sensitivity analysis will be based on OC.

Binary secondary endpoints in Part 1 will be analyzed using a similar method as the primary endpoint. Change from baseline in continuous secondary endpoints will be analyzed using MMRM with treatment, stratification factor of duration of prior MTX use, visit, and treatment-by-visit interaction as fixed effects, subject as random effect and baseline value as a covariate.

Pharmacokinetic and Immunogenicity: Adalimumab serum trough concentrations will be summarized by treatment arm at each time point using descriptive statistics including number of subjects, number of non-missing observations (nnmiss), 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. In addition, pharmacokinetic model-based analyses may be performed with the focus on apparent clearance (CL/F) and apparent volume of distribution (V/F).

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

Ultrasound: For the analysis of ultrasound endpoints in Part 1, similar MMRM model as described for the continuous secondary endpoints will be used and baseline weight will be included as an additional covariate in the MMRM model.

Safety: Safety analyses will be carried out using safety population, which includes all subjects that received at least one dose of study medication. Treatment-emergent 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, and up to within 70 days after the last dose of the study medication. All treatment emergent AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®). The number and percent of subjects experiencing AEs will be tabulated by system organ class and preferred term. In addition, a summary of AEs by severity and relationship to study drug will be presented. AEs, which are serious, severe, or life-threatening, which lead to premature study discontinuation will be listed and described in detail. Adverse events of special interest (AESI) will also be tabulated.

Statistical Methods (Continued):

Safety:

Observed values of vital signs and laboratory variables at each visit will be summarized for all treated subjects, and change from baseline in selected lab variables will be compared between treatment groups using a one way ANOVA. The last evaluation prior to the first dose of study drug will be used as Baseline for the analyses in Part 1. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) (Version 3) of Grade 3 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variables.

Section 5.5.2.2 Storage and Disposition of Study Drugs
First paragraph, fifth sentence previously read:

Malfunctions or any temperature excursion must be reported to the Sponsor immediately.

Has been changed to read:

Malfunctions and temperature excursions must be reported to the Sponsor immediately.

Section 5.5.7 Drug Accountability
Third paragraph
Fourth, fifth, sixth, seventh, and eighth sentence previously read:

Empty boxes, bottles and returned Sharps containers will be retained (unless prohibited by local law) until the site monitor is on site to confirm the returned medication. Site monitors and site staff will complete study medication accountability via IRT, source documents, subject dosing diaries, empty IP boxes, bottles and by visually inspecting the syringes and/or pens in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the site monitor has verified drug accountability at the site, the site staff and site monitor will document that the used pre-filled syringes and/or pens have been destroyed, using appropriate biohazard precautions, when appropriate.

Has been changed to read:

Site staff will complete study medication accountability in IRT, using source documents, subject dosing diaries, empty IP boxes, bottles and by visually inspecting the syringes and/or pens in the Sharps container whenever possible. Used Sharps containers should

never be opened. The site monitor will verify drug accountability either at the site or during remote monitoring and will complete the reconciliation in IRT. The site staff will document that the used pre-filled syringes and/or pens have been destroyed, using appropriate biohazard precautions, when appropriate.

Section 6.1.5
Fourth paragraph
"Primary Therapeutic Area Medical Director:" previously read:

[redacted], MD PhD
[redacted]
Global Medical Affairs Rheumatology
AbbVie
Dolenjska cesta 242c
Ljubljana SI-1000
Slovenia

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

Has been changed to read:

[redacted], MD
[redacted]
Global Medical Affairs Rheumatology
AbbVie
[redacted]
26525 North Riverwoods Blvd
Mettawa, IL 60045

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

Section 8.1.1 Analysis Population
First paragraph, first sentence previously read:

The primary and secondary effectiveness variables will be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication.

Has been changed to read:

The primary and secondary efficacy endpoints will be analyzed for the intent-to-treat (ITT) population, defined as all subjects who were randomized and received at least one dose of study medication.

Section 8.1.1. Analysis population
Frist paragraph, last sentence previously read:

In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary effectiveness variable may be conducted on the per protocol population, which consists of all ITT subjects who entered the randomized period of the study and did not meet any major protocol violation during the Part 1 of the study.

Has been changed to read:

In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary efficacy endpoint may be conducted on the per protocol population if deemed necessary. The Per Protocol population consists of all ITT subjects who entered the randomized period of the study and did not meet any major protocol violation during the Part 1 of the study.

Section 8.1.2 Statistical and Analytical Plan
Second, third, fourth, fifth, sixth and seventh paragraph previously read:

Unless otherwise stated, all statistical tests will be conducted at $\alpha = 0.05$ level (2-sided). Descriptive statistics will be provided including but not limited to the number of

observations, mean, standard deviation, median, minimum and maximum for continuous variables; and counts and percentages for discrete variables.

Statistical comparisons for the primary and secondary effectiveness endpoints will be performed at Week 16 between the Part 1 treatment groups. No multiplicity adjustment will be performed for the statistical tests.

An interim database lock is planned when all randomized subjects have completed Week 16 (Part 1) of the study. The 16 week study results (through Week 16) will be based on this database lock.

Data from the subsequent period (Part 2) will be reported at the completion of the study by Part 2 treatment groups.

The last available pre-treatment values recorded on or before Day 1 (the first dose of Part 1) will be considered as the Baseline value. All subsequent study visits will be determined in reference to the baseline.

To account for missing data for the discrete effectiveness endpoints, a non-responder imputation approach (NRI) will be used, i.e., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder. The last observation carried forward (LOCF) rule will be used to impute missing continuous effectiveness endpoints. That is, the subject's last non missing value assessed in the study while on study drug will be used in the analysis. In addition, an analysis using all observed data adjusting for baseline values will be performed as a sensitivity analysis for the effectiveness endpoints, using mixed-effects model repeated measures (MMRM) for continuous variables and logistic random-effect model for binary endpoints.

Has been changed to read:

Unless otherwise stated, all statistical tests will be conducted at $\alpha = 0.05$ level (2-sided). Descriptive statistics will be provided including but not limited to the number of

observations, mean, standard deviation, median, minimum and maximum for continuous endpoints; and counts and percentages for binary endpoints.

A Week 16 database lock is planned when all randomized subjects have completed Week 16 (Part 1) of the study. The Week 16 study results (through Week 16) will be based on this database lock. Statistical comparisons for the primary and secondary efficacy endpoints will be performed at Week 16 between the Part 1 treatment groups. No multiplicity adjustment will be performed for the statistical tests since there is only one primary endpoint.

Data from the subsequent period (Part 2) will be reported at the completion of the study by Part 2 treatment groups.

The last available pre-treatment values recorded on or before Day 1 (the first dose of Part 1) will be considered as the Baseline value for efficacy analysis. All subsequent study visits will be determined in reference to the baseline.

To account for missing data for the binary efficacy endpoints, a non-responder imputation approach (NRI) will be used, i.e., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder. For continuous endpoints, the Mixed-effects Model Repeated Measures (MMRM) analysis based on all observed data will be used.

Section 8.1.3 Analysis of Demographic Data and Baseline Disease Characteristics
First paragraph previously read:

Demographic and Baseline characteristics will be summarized and compared among treatment groups. The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables; and treatment group homogeneity will be assessed using a one-way analysis of variance (ANOVA) model using treatment, as the independent factor. Discrete variables will be summarized via counts and percentages; and treatment group homogeneity will be evaluated using the appropriate chi-square test.

Has been changed to read:

Demographic and Baseline characteristics will be summarized by treatment groups. The number of observations, mean, standard deviation, median, minimum and maximum will be summarized for continuous variables; Binary endpoints will be summarized via counts and percentages.

Section 8.1.4.1.1 Primary Analysis of Primary Efficacy Endpoint
Delete: Section title

8.1.4.1.1 Primary Analysis of Primary Efficacy Endpoint

Section 8.1.4.1.1 Primary Analysis of Primary Efficacy Endpoint
Second paragraph previously read:

The null hypothesis is that there is no difference in response rates between the adalimumab + MTX and MTX groups; the alternative hypothesis is that the response rates between the treatment groups are different. The response rates will be tested using a Cochran-Mantel-Haenszel (CMH) test adjusting for strata (duration of baseline use of MTX at 15 mg ew). Stratum is defined as the duration of baseline MTX 15 mg ew use of ≤ 3 months or > 3 months.

Has been changed to read:

The null hypothesis is that there is no difference in response rates between the adalimumab + MTX and MTX groups; the alternative hypothesis is that the response rates between the treatment groups are different. The response rates will be tested using a Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factor of the duration of prior (to screening) use of MTX at 15 mg ew. The stratification factor is defined as the duration of prior MTX 15 mg ew use of ≤ 3 months or > 3 months.

Sensitivity analyses will be conducted using the same method described above using observed cases (OC).

Section 8.1.4.1.2 Secondary Analysis of Primary Efficacy Endpoint
Delete: section title and text

8.1.4.1.2 Secondary Analysis of Primary Efficacy Endpoint

Secondary analyses of the primary endpoint will be conducted using all observed cases up to Week 16. Logistic regression model with stratum, treatment, visit, and treatment-by-visit interaction as fixed effects, subject as random intercept and baseline as covariate will be employed.

Section 8.1.4.2 Analyses of Secondary Efficacy Variables
Previously read:

A complete list of secondary effectiveness variables is provided in Section 5.3.3.2. Discrete secondary variables will be summarized using count and percentages and will be compared between treatment groups using CMH test.

Continuous secondary variables will be summarized by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum). Change from Baseline in the continuous variables will be analyzed using analysis of covariance (ANCOVA) with treatment as fixed effect and baseline value as a covariate for LOCF imputation. MMRM will be used for observed cases with stratum, treatment, visit, and treatment-by-visit interaction as fixed effects, subject as random effect and baseline value as covariate.

Has been changed to read:

A complete list of secondary efficacy endpoints is provided in Section 5.3.3.2. Binary secondary endpoints in Part 1 will be summarized using count and percentages and will be compared between treatment groups using CMH test adjusting for the stratification factor of the duration of prior use of MTX.

MDA at Week 32 is a Part 2 endpoint and it will be summarized by four treatment regimens. No statistical testing will be performed.

For the continuous secondary endpoints, the change from baseline at Week 16 will be analyzed using MMRM with treatment, stratification factor of prior MTX use, visit, and treatment-by-visit interaction as fixed effects, subject as random effect and baseline value as a covariate. The MMRM analysis is based on all observed data. The LS mean, 95% CI and standard error for each randomized treatment group, the LS mean of the treatment difference and its associated 95% CI and p-value from the MMRM model will be presented.

Section 8.1.4.3 Other Exploratory Analyses
Previously read:

Analysis for other effectiveness variables referenced in (Section 5.3.3.3) will be performed using similar methods to those described in Section 8.1.4.2.

For ultrasound assessment, baseline weight will also be included as additional covariate in ANCOVA and MMRM.

Has been changed to read:

Analysis for other efficacy endpoints referenced in (Section 5.3.3.3) will be performed using similar methods to those described in Section 8.1.4.2.

For ultrasound assessment in Part 1, baseline weight will also be included as additional covariate in MMRM.

Section 8.1.5 Statistical Analyses of Safety
First paragraph, last sentence previously read:

Treatment-emergent, and pre- and post-treatment AEs will be summarized and reported.

Has been changed to read:

Treatment-emergent AEs will be summarized and reported.

Section 8.1.5 Statistical Analyses of Safety
Last paragraph previously read:

Mean change in vital signs and laboratory variables at each visit as compared to baseline will be summarized for all treated subjects, and compared between treatment groups using a one way ANOVA. The last evaluation prior to the first dose of study drug will be used as Baseline 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 Baseline according to the normal range will also be provided for laboratory variable.

Has been changed to read:

Observed values of vital signs and laboratory variables at each visit will be summarized for all treated subjects, and change from baseline in selected lab variables will be compared between treatment groups using a one way ANOVA. The last evaluation prior to the first dose of study drug will be used as Baseline for the analyses in Part 1. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) (Version 3) of Grade 3 or higher will be provided. Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variable.

Section 8.1.6 Subject Disposition and Study Drug Exposure
First paragraph, first sentence previously read:

The number of subjects will be tabulated by investigator site and overall for the following categories: randomized, ITT population, completed (e.g., Part 1), and discontinued for each treatment group and for the total sample as appropriate.

Has been changed to read:

The number of subjects will be tabulated overall for the following categories: randomized, ITT population, completed (e.g., Part 1), and discontinued for each treatment group and for the total sample as appropriate.

Section 8.2 Determination of Sample Size
Last sentence previously read:

Assuming an MDA response rate of 40% in the adalimumab + MTX group and 20% in the escalated MTX group, a total sample size of 240 subjects, 120 subjects per arm, will provide at least 90% statistical power to detect the difference between the two treatment groups by a 2-sided Cochran-Mantel-Haenszel (CMH) test with a significance level of 0.05, allowing approximately 10% dropout.

Has been changed to read:

Assuming an MDA response rate of 40% in the adalimumab + MTX group and 20% in the escalated MTX group, a total sample size of 240 subjects, 120 subjects per arm, will provide at least 90% statistical power to detect the difference between the two treatment groups with a significance level of 0.05, allowing approximately 10% dropout.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Global Medical Affairs
		Global Medical Affairs
		Clinical Pharmacology & Pharmacometrics
		Statistics
		Bioanalysis
		Clinical Program Development

Has been changed to read:

Name	Title	Functional Area
[redacted]		Global Medical Affairs
		Global Medical Affairs
		Clinical Pharmacology & Pharmacometrics
		Statistics
		Bioanalysis
		Clinical Program Development
		Statistics