# 1.0 Title Page

## Clinical Study Protocol W14-406

## Concomitant longitudinal evaluation of adalimumab with methotrexate in the real world: the CLEAR study

## Amendment 2

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| AbbVie Investigational Products: | Adalimumab and Methotrexate |
| Date: | 22 April 2016 |
| Development Phase: | 3b |
| Study Design: | Multicenter, Single Arm, Open-Label, Longitudinal Study |
| EudraCT Number: | n/a |
| Investigator(s): | Investigator information on file at AbbVie |
| Sponsor: | AbbVie Corporation<br>8401, Trans-Canada Highway<br>Saint-Laurent, Quebec<br>H4S 1Z1, CANADA |
| Sponsor/Emergency Contact: | [redacted] |

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 | 12 March 2014 |
| Amendment 1 | 02 July2015 |

The purpose of this amendment is to incorporate the changes summarized below.

- **Applied administrative changes throughout protocol.**
  *Rationale for change: Text was revised to improve consistency and readability, and/or provide clarification.*

- **Number of Subjects to be Enrolled and number of Study Sites** were changed throughout the protocol.
  *Rationale for change: Due to low recruitment rate, the study population sample size was reviewed from approximately 200 to approximately* 50, and number of study sites clarified to approximately 25.*Changed to reflect to the current standard protocol template and to be consistent throughout protocol.*

- **Section 1.2, Synopsis.** Updated
  *Rationale for change: Synopsis was revised to be consistent with Amendment 2 revisions.*

- **Section 5.2.1, Inclusion Criteria**: **Criteria 5** updated.
  *Rationale for change: Criteria updated as per AbbVie latest protocol standard text and add precision to the inclusion of female of childbearing potential and male subject with childbearing potential female partner.*

- **Section 5.2.2, Exclusion Criteria**: **Criteria 17** added.
  *Rationale for change: Criteria added as per AbbVie latest protocol standard text and to clarify exclusion in regards to male subject considering fathering a child or donating sperm*

- **Section 5.2.4, Contraception Recommendations and Pregnancy Testing**: new
  *Rationale for change: Section added as per AbbVie latest protocol standard text and to add precision to acceptable contraception.*

- **Section 5.3.1.1, Study Procedures**: **Hepatitis B and Hepatitis C Testing.**
  *Rationale for change: Text updated to clarify exclusion of subjects with a positive HBc Ab Total test, indicating a previous Hep B exposure, link to a risk of reactivation or worsening of hepatitis B with MTX.*
- **Section 5.3.1.1, Study Procedures**: **Pregnancy Tests.**
  *Rationale for change: Addition of pregnancy tests at week 8 and 16 due to methotrexate embryotoxicity, and teratogenic effects and AbbVie latest protocol standard text.*
- **Section 8.2, Determination of Sample Size**. Updated.
  *Rationale for change: Section revised to reflect modification of study sample size .*

## 1.2 Synopsis

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| **AbbVie Corporation** | **Protocol Number:** W14-406 |
| **Name of Study Drugs:** Adalimumab and Methotrexate | **Phase of Development:** 3b |
| **Name of Active Ingredients:** Adalimumab and Methotrexate | **Date of Protocol Synopsis:** 22/Apr/2016 |
| **Protocol Title:** Concomitant longitudinal evaluation of adalimumab with methotrexate in the real world: the CLEAR study | |
| **Objective(s):**<br><br>Primary objective:<br><br>To determine the proportion of primary and secondary sub-optimal responders to adalimumab (ADA) monotherapy[1] (sub-optimal responders defined as subjects with an unsatisfactory response to psoriasis (Ps) treatment based on Investigator assessment)[2] with a PGA $\geq$ 3, and a PASI $\geq$ 5.0 who have a satisfactory response after 16 weeks of treatment with ADA/methotrexate (MTX) combination therapy, based on Investigator and subject satisfaction assessments (using satisfaction questionnaires).<br><br>Secondary objectives:<br><br>• To determine the proportion of primary and secondary sub-optimal responders to ADA monotherapy[1] (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) with a PGA $\geq$ 3 and a PASI $\geq$ 5.0 who reach PASI 50, PASI 75 and PASI 90 16 weeks after initiation of ADA/MTX combination therapy;<br>• To define the demographic and clinical profile of subjects benefiting from ADA/MTX combination therapy;<br>• To determine the magnitude, timing and maintenance of the benefit of adding MTX to ADA by assessing Investigator/subject satisfaction with treatment, PGA, PASI and Dermatology Life Quality Index (DLQI) at 8, 16 and 24 weeks after addition of MTX to therapy;<br>• To determine change in DLQI from baseline in subjects initiated on ADA/MTX treatment;<br>• To determine change in serum levels of ADA following addition of MTX and to characterize a possible correlation with changes in Investigator/subject satisfaction with treatment, PGA, PASI and DLQI over the study period. Serum levels will be evaluated at baseline (initiation of ADA+MTX) and at weeks 8, 16 and 24. | |
| **Investigator(s):** Multicenter | |

[1] Note that subjects may also be receiving topical treatments if they were prescribed prior to enrolment in the study
[2] Investigator assessment based on a questionnaire response; see Satisfaction questionnaire section

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| **Study Site(s):** Approximately 25 Canadian sites |
| **Study Population:** Adult subjects 18 years of age or older, with a clinical diagnosis of moderate to severe Ps for at least 6 months who have been receiving ADA monotherapy at a dose of 40 mg every-other-week (eow) or greater for at least 16 weeks and who, in the opinion of the treating Investigator, have a sub-optimal response to treatment, or have not maintained an initial positive response (secondary sub-optimal responders) (sub-optimal response and secondary sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) AND have a PGA score of $\geq$ 3 (or at least moderate disease) and a PASI of $\geq$ 5.0. |
| **Number of Subjects to be Enrolled:** Approximately 50 |
| **Methodology:** The study entails a 24-week treatment period and a 70-day safety follow-up period. Subjects, who in the opinion of the Investigator are not responding optimally to ADA monotherapy (40 mg eow or greater) at least 16 weeks after initiating treatment (primary sub-optimal responders) or who, after an initial positive response to ADA monotherapy (40 mg eow or greater) have failed to maintain an optimal level of response (secondary sub-optimal responders) (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) and have a PGA $\geq$ 3 and a PASI $\geq$ 5 will be potentially eligible for participation in the study. Potential subjects receiving ADA 40 mg once weekly will only be eligible for the study after a wash-out period of 8 weeks on ADA 40 mg eow. Following identification of potential subjects, the Investigator will arrange a pre-screening visit to discuss treatment status with the subject and outline the proposed study with the understanding that the subject must meet all inclusion criteria before participation. If subjects provide written consent, they will then complete a satisfaction questionnaire, and PGA and PASI status will be determined at a screening visit and inclusion/exclusion criteria assessed. Subjects eligible for participation in the study must have a PGA score of $\geq$ 3 and a PASI of $\geq$ 5.<br><br>Data collected at a baseline visit will include: subject demographics, disease history, comorbidities, vital signs, laboratory investigations, PGA, PASI and DLQI scores and serum levels of ADA. Subjects will continue to self-administer ADA (40 mg eow) but will have oral MTX added to their treatment at a dose to be defined by the Investigator. At site visits 8, 16 and 24 weeks after initiation of ADA/MTX, the following parameters will be assessed: physician assessment of disease status (using a satisfaction questionnaire); subject self-assessment of disease status (using a satisfaction questionnaire); PGA; PASI; DLQI; adverse events (AEs); serum levels of ADA.<br><br>Satisfaction questionnaire: Both Investigators and subjects will be asked how satisfied they are with the Ps control provided by the subject's current treatment. The provided responses will be: completely dissatisfied; moderately dissatisfied; slightly satisfied; highly satisfied; completely satisfied. Subjects with an Investigator assessment of completely or moderately dissatisfied with treatment will be categorized as a sub-optimal responder.<br><br>The 70-day safety follow-up period begins from the last dose of ADA. Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator in consultation with the AbbVie Medical Monitor. |

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

**Main Inclusion:**

1. Subjects who have been on ADA monotherapy (40 mg eow or greater) for at least 16 weeks but who in the opinion of the Investigator have shown a sub-optimal response to treatment and have a PGA of $\geq$ 3 and a PASI of $\geq$ 5; or
   Subjects who after an initial positive response to ADA monotherapy (40 mg eow or greater) have failed to maintain an optimal level of response, based on the opinion of the Investigator, and have a PGA of $\geq$ 3 and a PASI of $\geq$ 5;
2. Subjects who are receiving 40 mg ADA once weekly must be on ADA 40 mg eow for 8 weeks prior to screening;
3. Subjects with at least a 6 month history of chronic plaque Ps;
4. Subjects greater than or equal to 18 years of age;
5. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile or is of childbearing potential and is practicing birth control;
6. The results of the serum pregnancy test performed during the Screening Period and urine pregnancy test performed at the Baseline Visit must be negative;
7. Subject is judged to be in good general health as determined by the Principal Investigator;
8. Subjects must be evaluated for latent TB infection;
9. Subjects must be able and willing to provide written informed consent and comply with the requirements of the study protocol;
10. Subjects must be willing and able to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections.

**Main Exclusion:**

1. Subject has any contraindications to MTX or ADA;
2. Subject has a previous failed response or poor tolerance to ADA;
3. Subject has a poorly controlled medical condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study;
4. Subject has a history of clinically significant hematologic, renal or liver disease;
5. Subject has a history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease and/or diagnosis of central demyelinating disease;
6. Subject has evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix;
7. Subject has a history of listeriosis, histoplasmosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous (iv) anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit;
8. Subject is known to have immune deficiency, history of HIV or is immunocompromised;
9. Subject currently uses or plans to use anti-retroviral therapy at any time during the study;
10. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study or for 150 days after the last dose of study medication;

**Main Exclusion (contd.):**

11. Subject has a history of clinically significant drug or alcohol usage in the last year or cannot maintain an alcohol intake of 30 g a day or less throughout the study (one standard drink is defined as 180 mL/6 oz (approx. 10 g) of wine, 360 mL/12 oz (approx. 15 g) of regular beer, or 45 mL/1.5 oz (approx. 10 g) of spirits;
12. Screening clinical laboratory analyses show any of the following abnormal laboratory results:
    - Aspartate transaminase (AST) or alanine transaminase (ALT) > 2x the upper limit of normal (ULN);
    - Serum total bilirubin > 1.5 mg/dL (> 26 micromol/L), except for subjects with Gilbert's Syndrome;
    - Creatinine > 1.5 mg/dL (133 micromol/L) in subjects ≤ 65 years old and > upper limit of normal range in subjects > 65;
    - Positive Hepatitis B or C serology indicative of previous or current infection.
13. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study;
14. The following treatments are prohibited for all subjects during the study:
    1. Phototherapy (PUVA (within 4 weeks of the Baseline Visit) and/or UVB (within 2 weeks of the Baseline Visit);
    2. Other biologic therapies (including any other anti-TNF) within 4 weeks of the Baseline Visit;
    3. Any investigational agents of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline visit ;
    4. Any other systemic drug therapies for Ps within 4 weeks of the Baseline Visit;
    5. Oral or injectable corticosteroids, new prescription topical therapies, or changes in the concentration of current prescription topical therapies (including corticosteroids) that are being used, within 2 weeks of the Baseline Visit. Subjects may continue using previously prescribed topical therapies (including corticosteroids) during the study.
15. Prior exposure to biologics that have a potential or known association with Progressive multifocal leukoencephalopathy PML (i.e., natalizumab (Tysabri®) or rituximab (Rituxan®));
16. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study;

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| **Investigational Product(s):** | ADA and MTX |
| **Dose(s):** | ADA: 40 mg eow beginning at study Week 0 through Week 22.<br><br>MTX: Dose is up to the discretion of the investigator but recommended dose should be between 10 and 25 mg/week, beginning at Week 0 through Week 23. The minimum initial dose of MTX should be 10 mg/week. MTX dose can be increased at any time over the study period, based on the clinical judgment of the Investigator. |
| Mode of Administration: | ADA: SC injections self-administered by subjects via pens.<br><br>MTX: Oral administration. |
| **Reference Therapy:** | There is no reference therapy in this study |
| **Dose(s):** | |
| **Mode of Administration:** | |

**Duration of Treatment:** ADA will be administered for 24 weeks (last dose of ADA will be at Week 22); following this period decision to continue ADA will be at the discretion of the Investigator;

Study-related MTX will be administered for 24 weeks (last dose of MTX will be at Week 23); following this period decision to continue MTX will be at the discretion of the Investigator.

**Criteria for Evaluation:**

**Efficacy:** The primary efficacy endpoints will be:

- Based on investigator assessment, the proportion of subjects (primary and secondary sub-optimal responders) achieving a satisfactory response to ADA + MTX treatment after 16 weeks (satisfactory response defined as highly or completely satisfied with subject's therapy using the satisfaction questionnaire);
- Based on subject self-assessment, the proportion of subjects (primary and secondary sub-optimal responders) achieving a satisfactory response to ADA + MTX treatment after 16 weeks (satisfactory response defined as highly or completely satisfied with therapy using the satisfaction questionnaire).

Secondary efficacy endpoints will include:

- The proportion of subjects (primary and secondary sub-optimal responders) achieving 50%, 75%, 90% and 100% reductions in PASI at 8, 16 and 24 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- The proportion of primary sub-optimal responders achieving 50%, 75%, 90% and 100% reductions in PASI at 8, 16 and 24 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- The proportion of secondary sub-optimal responders achieving 50%, 75%, 90% and 100% reductions in PASI at 8, 16 and 24 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- The proportion of subjects on ADA 40 mg eow prior to baseline or 40 mg once weekly prior to wash-out achieving 50%, 75%, 90% and 100% reductions in PASI 16 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- Proportion of primary and secondary sub-optimal responders achieving a clinical response defined as a PGA of "Clear" or "Minimal" at 8, 16 and 24 weeks after initiation of ADA + MTX;
- DLQI scores at baseline (at initiation of ADA + MTX) and at weeks 8, 16 and 24;
- Change and percent change in DLQI from baseline to weeks 8, 16 and 24;
- Proportion of subjects with each of the five categories of satisfaction with treatment at baseline (at initiation of ADA + MTX) and at weeks 8, 16 and 24 (subject self-assessment and investigator assessment using the satisfaction questionnaires);
- Proportion of primary and secondary sub-optimal responders achieving a DLQI score of 0 or 1, at 8, 16 and 24 weeks after initiation of ADA + MTX;
- Serum levels of ADA in subjects at baseline (at initiation of ADA + MTX) and at weeks 8, 16 and 24.

**Safety:**

Safety analyses will be performed on all subjects who receive at least one dose of ADA + MTX. Incidence of AEs, changes in vital signs, physical examination results, and clinical laboratory tests will be assessed.

**Statistical Methods:**

**Efficacy:**

The primary analyses will be the proportion of subjects with Ps who have a satisfactory response to ADA + MTX treatment, based on a self-assessment by subjects and an assessment by the treating Investigator. Secondary analyses will include an evaluation of the efficacy of ADA + MTX in subjects with Ps and characterization of the possible relationship between serum levels of ADA and efficacy outcomes.

This study will have a 12 month recruitment period where it is anticipated that approximately 50 subjects will be recruited. With this sample size the proportion of responders, after 16 weeks of ADA + MTX therapy, based on an Investigator assessment and subject self-assessment, can be estimated within ± 4.9% with 95% confidence when the point estimate is 15%, within ± 6.4% with 95% confidence when the point estimate is 30%, or within ± 6.9% with 95% confidence when the point estimate is 50%.

Due to the recent enrollment plan change, this study will only enroll 50 patients or as the number of enrollment by 31-Dec-2016, With 50 subjects the same proportion of responders can be estimated within ± 9.9% with 95% confidence when the point estimate is 15%, within ± 12.7% with 95% confidence when the point estimate is 30%, or within ± 13.9% with 95% confidence when the point estimate is 50%.

The primary and secondary efficacy analyses will be conducted on the ITT population (subjects who receive at least one dose of ADA and MTX). The primary efficacy analyses will also be conducted for the following subgroups:

- Subjects defined as primary sub-optimal responders at baseline, based on Investigator assessment;
- Subjects defined as secondary sub-optimal responders at baseline, based on Investigator assessment.

For the primary and secondary efficacy analyses, sub-optimal responder imputation (imputing missing satisfaction data as "dissatisfied") will be used. In the event that greater than 5% of the satisfaction data are missing, last observation carried forward will also be carried out to impute the missing data in sensitivity analyses. Secondary outcomes will be analyzed using available data at each assessment point and changes over time will be estimated using a Mixed Model. Exploratory analysis to determine associations between ADA serum levels and PASI, PGA and DLQI scores will be carried out.

**Safety:**

All AEs, SAEs, and AEs leading to discontinuation will be collected during the study and up to 70 days after the last dose of ADA. Safety analyses will be carried out using the Safety Population. A treatment-emergent AE is defined as an event with onset or worsening after the first dose of study drugs (ADA + MTX) and within 70 days after the last dose of ADA. The number and percent of subjects experiencing treatment-emergent AEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-years) of SAEs, deaths and AEs leading to discontinuation from the study will be provided.

## 1.3 List of Abbreviations and Definition of Terms

**Abbreviations**

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| °C | Degrees Celsius |
| ADA | Adalimumab |
| AE | Adverse Event |
| ALT | Alanine Transaminase |
| ANA | Antinuclear Antibody |
| Anti-ds DNA | Anti-Double-Stranded Deoxyribonucleic acid |
| AS | Ankylosing Spondylitis |
| AST | Aspartate Transaminase |
| ATEMS | AbbVie Temperature Excursion Management System |
| BCG | Bacille Calmette-Guerin |
| BSA | Body Surface Area |
| BUN | Blood Urea Nitrogen |
| CD | Crohn's Disease |
| CNS | Central Nervous System |
| CRA | Clinical Research Associate (Monitor) |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CXR | Chest X-Ray |
| DLQI | Dermatology Life Quality Index |
| dsDNA | Double Stranded Deoxyribonucleic Acid |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMEA | European Agency for the Evaluation of Medicinal Products |
| Eow | Every other week |
| ESR | Erythrocyte Sedimentation Rate |
| FDA | US Food and Drug Administration |
| GCP | Good Clinical Practice |
| HAV-IgM | Hepatitis A virus immunoglobulin M |
| HBc Ab | Hepatitis B Core Antibody |
| HBs Ab | Hepatitis B Surface Antigen |

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| HBs Ag | Hepatitis B Surface Antigen |
| HBV | Hepatitis B Virus |
| HCV Ab | Hepatitis C virus antibody |
| HIV | Human Immunodeficiency Virus |
| hsCRP | Highly Sensitive C-Reactive Protein |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IGRAs | Interferon-Gamma Release Assays |
| INH | Isoniazid |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IVRS/IWRS | Interactive Voice Response System/Interactive Web Response System |
| LOCF | Last Observation Carried Forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Mg | Milligram |
| mL | Milliliter |
| MMR | Measles-Mumps-Rubella |
| MTX | Methotrexate |
| OPV | Oral Polio Vaccine |
| PASI | Psoriasis Area Severity Index |
| PCR | Polymerase Chain Reaction |
| PGA | Physician's Global Assessment |
| PK | Pharmacokinetic |
| PML | Progressive Multifocal Leukoencephalopathy |
| POR | Proof of Receipt |
| PPD | Purified Protein Derivative |
| Ps | Psoriasis |
| PsA | Psoriatic Arthritis |
| PUVA | Ultraviolet A with Psoralen |
| RA | Rheumatoid Arthritis |
| RBC | Red Blood Cells |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous (injection) |

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| SGOT | Serum Glutamic-oxaloacetic Transaminase |
| SGPT | Serum Glutamic-pyruvic Transaminase |
| TB | Tuberculosis |
| TNF-α | Tumor Necrosis Factor-Alpha |
| UC | Ulcerative Colitis |
| UV | Ultraviolet |
| RNA | Ribonucleic acid |

**Definition of Terms**

PASI 50 50% reduction in Baseline PASI score

PASI 75 75% reduction in Baseline PASI score

PASI 90 90% reduction in Baseline PASI score

PASI 100 100% reduction in Baseline PASI score

Sub-optimal response to therapy: Based on completely dissatisfied or moderately dissatisfied responses on the Satisfaction Questionnaire

Satisfactory response to therapy: Based on highly satisfied or completely satisfied responses on the Satisfaction Questionnaire

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## 3.0 Introduction

Psoriasis (Ps) is an immune-mediated, chronic, inflammatory skin disorder that impacts both physical and emotional aspects of an individual's quality of life and requires lifelong care (1,2). In addition, subjects with Ps are at an increased risk for clinical comorbidities including cardiovascular disease, metabolic syndrome, diabetes and lymphoproliferative malignancies that complicate overall disease management and can lead to significant reductions in life expectancy (2,3). There is also an increased risk of diseases with a related inflammatory origin, the most common being psoriatic arthritis (PsA), which can develop many years after the initial diagnosis of skin Ps (3). The age specific prevalence of Ps in Canada has been estimated at approximately 1.7% meaning that more than 500,000 Canadians suffer from the disease (2). Ps can occur at any age but most often develops between the ages of 15 and 25 and men and women are affected in equal proportions (4). Approximately 17% of patients previously diagnosed with Ps will have moderate to severe disease (5) and the estimated prevalence of PsA in a population with Ps is approximately 30% (6).

Although traditional systemic therapies such as methotrexate (MTX), cyclosporine and acitretin can be effective in treatment of Ps, they are associated with adverse events (AEs) which can limit their long-term use and also require extensive laboratory monitoring (1,2,4). However, biologic therapies, which specifically target the overactive immune system characteristic of Ps, have provided a significant advance in the treatment of this disease (4). These agents work by targeting specific steps in the inflammatory cascade (4). One of the key targets in this cascade is tumor necrosis factor (TNF), a cytokine that plays a role in the development of Ps (1,2,4). Several biologics (adalimumab (ADA), etanercept and infliximab) specifically target TNF by different mechanisms and all have demonstrated effectiveness in the treatment of Ps and other inflammatory diseases, including PsA, rheumatoid arthritis (RA), Crohn's disease (CD) and ankylosing spondylitis (AS) (2,7,8). ADA is a fully human monoclonal antibody that binds with high affinity and specificity to human TNF, neutralizing the biologic activities of the cytokine by blocking its interaction with cell surface TNF receptors, and suppressing the

downstream biologic responses (1). Currently in Canada, ADA is indicated for the treatment of RA, polyarticular juvenile idiopathic arthritis (JIA), PsA, AS, adult and pediatric CD, ulcerative colitis (UC), Ps, and hidradenitis suppurativa (HS) (9).

The efficacy and safety of ADA in Ps has been demonstrated in a number of Phase III trials (1,10,11,12). In the pivotal REVEAL clinical trial, subjects with moderate to severe plaque Ps receiving ADA (40 mg every other week (eow) after an initial 80 mg dose at baseline) had a week 16 Psoriasis Area and Severity Index (PASI) 75 response rate of 71% compared to 7% for subjects receiving placebo ($p<.001$); PASI 90 and 100 rates at week 16 were 45% and 20% with ADA compared to responses of 2% and 1% in placebo subjects, respectively ($p<.001$ for both comparisons) (1). Additional data from the REVEAL study showed that continuous treatment with ADA may be required to maintain the therapeutic response; when subjects with PASI 75 response at 33 weeks were randomized to placebo or continued ADA therapy, only 5% of the latter group lost adequate response (defined as <50% improvement in the PASI response relative to baseline and at least a 6-point increase in PASI score from week 33) by week 52 compared to 28% of subjects randomized to placebo ($p<.001$) (1). In an open label extension of the REVEAL study, ADA efficacy was generally well maintained for over 3 years in subjects who had a sustained PASI 75 response during the clinical trial (13).

Although TNF-α antagonists are effective in the treatment of inflammatory diseases, not all subjects respond to initial treatment and some may fail to maintain an initial positive response with prolonged therapy (8,14). This is particularly evident with infliximab and ADA and has been observed in RA, PsA, CD and AS (14,15). The mechanisms behind this loss of optimal response are not fully understood but there is evidence that one of the contributing factors is the development of antibodies against TNF-α antagonists which lower the serum drug concentration to sub-therapeutic levels (8,14,15). A recent meta-analysis of studies involving subjects with different immune-mediated inflammatory diseases found that antibodies against infliximab and ADA reduced overall drug response rates by 68% (8).

Antibodies against ADA have been shown to contribute to lower treatment response in RA, PsA, CD and AS (8, 14-20). However, information on the relationship between TNF inhibitor serum levels, antibodies and clinical response with respect to Ps is limited (8,14,15). It is clear that subjects with Ps can develop antibodies against ADA, although the actual reported proportions with an immune response is variable, ranging from 6% following treatment discontinuation and relapse (21), 8.8% in the pivotal Phase III REVEAL clinical trial (1) and 16% and 45% in two prospective observational studies (14,22,23). The latter studies showed that trough levels of ADA were positively associated with clinical response and were significantly lower in subjects with anti-ADA antibodies (14,22,23). For example, Lecluse et al. (22) found that in 29 Ps subjects (mean PASI at baseline, 15.5; disease duration 22 years; mean number of prior systemic therapies, 4.2) who were initiated on ADA, 45% had developed anti-ADA antibodies at 24 weeks. In these subjects, titers of anti-ADA antibodies were associated with low ADA serum levels which in turn correlated with low treatment response (22). A recent study by Mahil et al. (14) confirms that antibodies against ADA contribute to a poor treatment response in Ps; after 4 weeks, ADA serum levels were significantly higher in clinical responders compared to non-responders ($p=0.003$) and anti-ADA antibodies were detected in 25% of non-responders compared to none of the responders (14).

In addition to treatment failure, the presence of anti-TNF antagonist antibodies can lead to an increased risk of AEs such as acute or delayed infusion reactions which can decrease adherence to treatment regimens and lower treatment response (15).

Clinical responses to treatment failure in inflammatory diseases include dose escalation, concomitant administration of an immunosuppressant, or a switch to a different TNF antagonist (24-27). With ADA, dose escalation is accomplished by decreasing the dosing interval from two weeks to one week, and with respect to Ps, Leonardi et al. (24) found that 26.6% of subjects who initially failed ADA therapy (defined as subjects with a < PASI 50 response after 24 weeks) were PASI 75 responders 12 weeks after dose escalation. However, dose escalation is associated with increased treatment costs (24) and

means weekly injections for patients which may negatively impact patient compliance with treatment.

An alternative to dose escalation is the concomitant administration of an immunosuppressant such as MTX (8). There is evidence in RA that addition of MTX to ADA significantly increases clinical response (25,26). Krieckaert et al. (26) found that RA subjects using concomitant MTX developed anti-ADA antibodies less often than subjects not using MTX (Odds Ratio (OR) 0.20 (95% CI 0.12, 0.34, $p<0.001$) (26). Preliminary data from van den Reek et al. (27), based on a small number of subjects (n = 11), shows that subjects with Ps may also benefit from the addition of MTX to ADA therapy; in subjects with an insufficient response to ADA monotherapy (40 mg eow), addition of MTX (9.5 mg per week) increased the effectiveness of therapy.

The present study is designed to provide further information on the impact of adding MTX to ADA monotherapy in subjects with Ps who have failed to achieve an optimal response to initial ADA therapy or have not maintained an initial positive response to treatment. In addition to traditional clinical measures of disease activity, the study also incorporates a measure of the Investigator's satisfaction with treatment response in individual subjects, and each subject's personal level of satisfaction with treatment. This outcome measure reflects the most recent Canadian Ps treatment guidelines which emphasize "patient-centered Ps care" in real clinical practice and encourage treatment choice based not only on a potential effective clinical outcome but also on the subject's preference for a specific treatment (2). As a result, in the current study Investigator and subject satisfaction plays an important role both in defining subjects who have "failed" ADA monotherapy and in quantifying the response after addition of MTX to ADA therapy. In addition, although the clinical impact of addition of MTX to ADA therapy may result from a reduction in anti-ADA antibodies, this study focuses on ADA trough concentrations as a parameter rather than anti-ADA antibody levels. Measurement of anti-drug antibodies can be technically challenging and, depending on the assay, serum ADA can interfere with antibody measurements in a concentration dependent manner (29), complicating interpretation of the data. Because of the potential limitations associated

with antibody assays, the present study focuses on ADA serum concentrations and changes in levels after addition of MTX to therapy.

## 3.1 Differences Statement

This study is being conducted to assess the efficacy and safety of combination therapy with ADA and MTX in the treatment of Ps. While previous Phase II to Phase IV studies have been conducted on the use of ADA monotherapy (usually in combination with additional topical therapies) in treatment of Ps, this is one of the first to assess the impact of adding MTX to ADA therapy in subjects who have had a sub-optimal response to ADA alone. Furthermore, reflecting the most recent Canadian Ps treatment guidelines (2), which emphasize patient centered Ps care, this study includes subject and Investigator satisfaction with therapy as a primary endpoint, in addition to traditional measures of treatment response in Ps.

## 3.2 Benefits and Risks

ADA has generated extensive clinical and post-marketing data in a wide range of disease states including the dermatological indication of Ps (an approved indication in Canada). The safety profile of ADA in this and other approved indications is well established (9). The Investigator is referred to the current Investigator's Brochure where additional and more detailed information regarding potential risks and benefits of ADA can be found.

The potential benefit of this proposed study in Ps is the demonstration that the addition of MTX to ADA therapy is associated with a reduction in symptoms of Ps, an improvement in subject quality of life and an increase in satisfaction with therapy in subjects who have moderate to severe Ps but who are not responding optimally to ADA therapy alone. As Ps is associated with debilitating symptoms and has a substantial quality of life impact, any improvement in Ps symptoms with the addition of MTX could directly benefit patients.

Subjects in the study will have MTX added to their ADA therapy and therefore will have the added risk of AEs associated with MTX or the combination of MTX and ADA. The Investigator is referred to the current ADA Product Monograph (9) where detailed

information is provided on the risks associated with ADA and MTX in the treatment of approved indications in Canada are described. Investigators can assume that the risks associated with ADA and MTX in currently approved indications for inflammatory diseases can also be expected in the treatment of Ps. In addition, Investigators are referred to the Product Monograph for MTX for additional information on the risks associated with use of this immunosuppressant.

## 3.3 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.

## 3.4 Safety Information

ADA 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 rheumatoid arthritis. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with ADA can be

found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in patients 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.

# 4.0 Study Objective

## 4.1 Primary objective

To determine the proportion of primary and secondary sub-optimal responders to ADA monotherapy[3] (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment[4]) with a PGA $\geq$ 3 and a PASI $\geq$ 5 who have a satisfactory response after 16 weeks of treatment with ADA/MTX combination therapy, based on Investigator and subject satisfaction assessments.

## 4.2 Secondary objectives

- To determine the proportion of primary and secondary sub-optimal responders to ADA monotherapy (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) with a PGA $\geq$ 3 and a PASI $\geq$ 5 who reach PASI 50, PASI 75 and PASI 90 16 weeks after initiation of ADA/MTX combination therapy;
- To define the demographic and clinical profile of subjects benefiting from ADA/MTX combination therapy;
- To determine the magnitude, timing and maintenance of the benefit of adding MTX to ADA by assessing Investigator/subject satisfaction with treatment, PGA, PASI

[3] Note that subjects may also be receiving topical treatments if they were prescribed prior to enrolment in this study
[4] Investigator assessment based on a questionnaire response; see Satisfaction questionnaire section

and Dermatology Life Quality Index (DLQI) at 8, 16 and 24 weeks after addition of MTX to therapy;

- To determine change in DLQI from baseline in subjects initiated on ADA/MTX treatment;
- To determine change in serum levels of ADA following addition of MTX and to characterize a possible correlation with changes in Investigator/subject satisfaction with treatment, PGA, PASI and DLQI over the study period. Serum levels will be evaluated at baseline (initiation of ADA+MTX) and at weeks 8, 16 and 24.

# 5.0 Investigational Plan

## 5.1 Overall Study Design and Plan: Description

This is a multicenter, single arm, open label longitudinal study. The study entails a -screening period up to 35 days, a 24-week treatment period and a 70-day safety follow-up period. Subjects, who in the opinion of the Investigator are not responding optimally to ADA monotherapy (40 mg eow or greater) at least 16 weeks after initiating treatment (primary sub-optimal responder) or who, after an initial positive response to ADA monotherapy (40 mg eow or greater) have failed to maintain an optimal level of response (secondary sub-optimal responders) (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) and who have a PGA score of $\geq$ 3 and a PASI of $\geq$ 5 will be potentially eligible for participation in the study.

For potential subjects on ADA 40 mg once weekly, the Investigator will arrange a pre-screening visit to discuss treatment status with the subject and outline the proposed study with the understanding that the subject must meet all inclusion criteria before participation. If the potential subjects signed the consent form, they will start the washout period and the subjects will be eligible for the screening visit after 8 weeks on ADA 40 mg eow.

If subjects provide written consent, they will then complete a satisfaction questionnaire (Appendix C), and PGA and PASI status will be determined at a screening visit and inclusion/exclusion criteria will be assessed. In addition to the Investigator assessment of

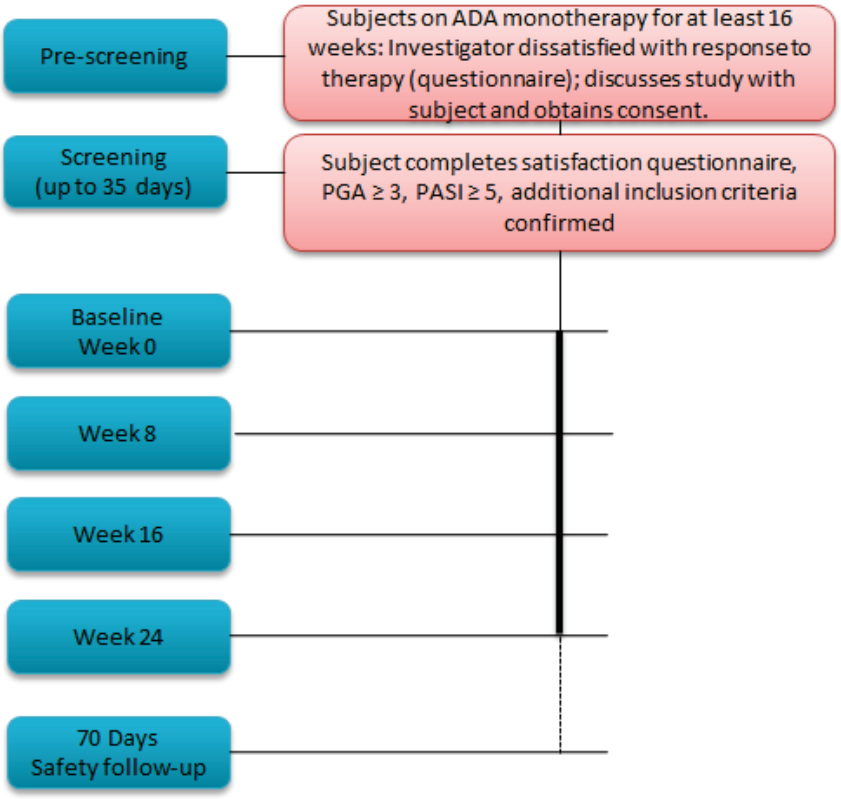
sub-optimal response to current ADA monotherapy, subjects eligible for participation in the study must have a PGA score of $\geq$ 3 and a PASI of $\geq$ 5. Data collected at a screening visit will include: subject demographics, disease history, comorbidities, vital signs, laboratory investigations and PGA, PASI and DLQI scores. Starting at the baseline visit (Day 0), subjects will continue to self-administer ADA (40 mg eow) and will have oral MTX added to their treatment at a dose to be defined by the Investigator (between 10 mg and 25 mg per week). All subjects will also receive the non-investigational medicinal product oral folic acid as a dietary supplement since MTX acts as a folic acid antagonist. The folic acid tablets will be provided by the Investigator at a dose of 1.0 mg per day. The required folic acid dose must be taken every day of the week except on the day when MTX is taken. The Investigator will provide specific instructions on the number of folic acid tablets each subject should take.

In the event a subject forgets to take the tablets or takes more or less than is required, they will be instructed to contact the Investigator for guidance. Unused folic acid tablets should be returned to the investigative site and accounted for to assess subject's compliance.

At site visits 8, 16 and 24 weeks after initiation of ADA/MTX, the following parameters will be assessed: Investigator assessment of disease status (using a satisfaction questionnaire); subject self-assessment of disease status (using a satisfaction questionnaire); PGA; PASI; DLQI; AEs; serum levels of ADA. A schematic of the study design is shown in Figure 1.

The 70-day safety follow-up period begins from the last dose of ADA. Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the Investigator in consultation with the AbbVie Medical Monitor.

**Figure 1: Study Design Schematic**




The study was designed to enroll 50 subjects to meet scientific 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.

## 5.2 Selection of Study Population

### 5.2.1 Inclusion Criteria

1. Subjects who have been on ADA monotherapy (40 mg eow or greater) for at least 16 weeks but, who in the opinion of the Investigator, have shown a sub-optimal response to treatment (sub-optimal response defined as subjects with an unsatisfactory response to treatment, based on Investigator assessment) and have a PGA of $\geq$ 3 and a PASI of $\geq$ 5; or
   Subjects who after an initial positive response to ADA monotherapy (40 mg eow or greater) have failed to maintain an optimal level of response, based on the opinion of the Investigator (sub-optimal response defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) and have a PGA of $\geq$ 3 and a PASI of $\geq$ 5;
2. Subjects who are receiving 40 mg ADA once weekly must be on ADA 40 mg eow for 8 weeks prior to screening;
3. Subjects with at least a 6 month history of chronic plaque Ps;
4. Subjects greater than or equal to 18 years of age;
5. If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or is of childbearing potential and is practicing one of the following methods of birth control throughout the study and for 150 days after the last dose of study drug:
   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD);
   - Contraceptives (oral, parenteral, transdermal) for three months prior to study drug administration;
   - A vasectomized partner.

   If the male subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 150 days after the last dose of study drug to practice the protocol specified contraception (Section 5.2.4).

6. The results of the serum pregnancy test performed during the Screening Period and urine pregnancy test performed at the Baseline Visit must be negative for females of childbearing potential;

7. Subject is judged to be in good general health as determined by the Investigator based upon the results of medical history, laboratory profile, physical examination, chest X-ray (CXR), and 12-lead electrocardiogram (ECG) performed during Screening;
8. Subjects must be evaluated for latent TB infection with a purified protein derivative (PPD) test or QuantiFERON-TB test and chest X-ray. For this protocol, evidence of latent TB infection is defined as an induration (not erythema) of 5 mm or greater, 48-72 hrs after placement or a positive QuantiFERON-TB test result. Subjects who demonstrate evidence of latent TB infection, irrespective of Bacille Calmette - Guérin (BCG) vaccination status, and negative CXR findings for active TB and/or suspicious CXR findings, will be allowed to participate in the study provided that one of the following conditions are satisfied;
    - Prophylactic treatment is initiated at least two weeks prior to administration of study drug; however the course of prophylaxis does not need to be completed prior to the onset of study drug. Prophylactic treatment will be according to the United States Centers for Disease Control [CDC] recommended preventive therapy for TB or per local guidelines. Prophylactic treatment should be captured on the concomitant medications page in the CRF and in the source documents
    - Subject has documented completion of a full course of TB prophylaxis
9. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol;
10. Subjects must be willing and able to self-administer subcutaneous (SC) injections or have a qualified person available to administer SC injections.

These inclusion criteria reflect the subject population necessary to fulfill the study design. In particular, the criteria mean that subjects showing a sub-optimal response to ADA monotherapy, based primarily on Investigator assessment, will be recruited for the study. To expand the potential subject pool, the inclusion criteria include primary and secondary sub-optimal responders to ADA therapy and includes subjects who are receiving more than 40 mg ADA eow (i.e., 40 mg once weekly). However, in the latter case, subjects must be on ADA 40 mg eow for at least 8 weeks prior to screening. This wash-out phase should begin after subject consent.

### 5.2.2 Exclusion Criteria

1. Subject has any contraindications to MTX or ADA;
2. Subject has a previous failed response or poor tolerance to ADA;
3. Subject has a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the Investigator, would put the subject at risk by participation in the study;
4. Subject has a history of clinically significant hematologic (e.g., severe anemia, leukopenia, thrombocytopenia), renal or liver disease (e.g., fibrosis, cirrhosis, hepatitis);
5. Subject has history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease and/or diagnosis of central demyelinating disease;
6. Subject has evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix;
7. Subject has a history of listeriosis, histoplasmosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous (iv) anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit;
8. Subject is known to have immune deficiency, history of HIV or is immunocompromised;
9. Subject currently uses or plans to use anti-retroviral therapy at any time during the study;
10. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study or for 150 days after the last dose of study medications;
11. Subject has a history of clinically significant drug or alcohol usage in the last year (12 months) or cannot maintain an alcohol intake of 30 g a day or less throughout the study. One standard drink is defined as 180 mL/6 oz (approx. 10 g) of wine, 360 mL/12 oz (approx. 15 g) of regular beer, or 45 mL/1.5 oz (approx. 10 g) of spirits;
12. Screening clinical laboratory analyses show any of the following abnormal laboratory results:
    - Aspartate transaminase (AST) or alanine transaminase (ALT) >2x the upper limit of normal (ULN);

- Serum total bilirubin > 1.5 mg/dL (> 26 micromol/L), except for subjects with Gilbert's Syndrome;
- Creatinine > 1.5 mg/dL (133 micromol/L) in subjects ≤ 65 years old and > ULN range in subjects > 65;
- Positive Hepatitis B or C serology indicative of previous or current infection.

13. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study;
14. The following treatments are prohibited for all subjects during the study:
    - Phototherapy (PUVA (within 4 weeks of the baseline visit) and/or UVB (within 2 weeks of the baseline visit));
    - Other biologic therapies (including any other anti-TNF) within 4 weeks of the baseline visit (except for ADA);
    - Any investigational agents of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to the Baseline visit;
    - Any other systemic drug therapies for Ps, including cyclosporine, retinoids, and fumaric acid esters, within 4 weeks of the baseline visit;
    - Oral or injectable corticosteroids, new prescription topical therapies (including shampoos with corticosteroids), or changes in the concentration of current prescription of topical therapies (including corticosteroids) that are being used, within 2 weeks of the baseline visit. However, subjects may continue using previously prescribed topical therapies (including corticosteroids) during the study. Inhaled corticosteroids are allowed. .
15. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab (Tysabri®) or rituximab (Rituxan®);
16. Subjects with any active viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study.
17. Male subject who is considering fathering a child or donating sperm during the study or for approximately 150 days after the last dose of study drug.

These criteria reflect the usual exclusion criteria in Phase III studies assessing ADA and MTX in the treatment of Ps.

### 5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of screening, 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.

The AbbVie Medical Monitor identified in Section 6.1.5 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

In addition, for subjects age ≤ 30 with a reported malignancy event during the study, 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 dosing information to estimate total exposure, will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy AE, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

#### 5.2.3.1 Prior Therapy

Anti-Ps systemic therapy and phototherapy treatment since initial diagnosis and topical therapies since the last six months prior to Screening (as determined through medical history records or through subject interview), and any administered treatments within the past 28 days prior to Screening should also be recorded on the appropriate CRF.

Each vaccine administered to the subject within 28 days prior to screening should be listed as a concomitant medication. Live vaccines are prohibited (Section 5.2.3.3).

For subjects previously treated with biologics e.g., etanercept, and/or infliximab, the duration of therapy, maximum dose, reason for use and reason(s) for termination of treatment with these products should be documented.

#### 5.2.3.2 Concomitant Therapy

Any medication, including vaccines, the subject receives during the study (and within 28 days of the Screening visit) should be recorded. Subjects may continue using previously prescribed topical therapies (including corticosteroids) during the study. However, application of these topical therapies for Ps should not occur within 24 hours of a study visit so as not to interfere with clinical assessments for Ps.

All subjects in the study will be taking oral MTX (between 10 mg and 25 mg per week) and should also take a dietary supplement of oral folic acid every day, except on the day the subject is taking MTX over the study period.

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

#### 5.2.3.3 Prohibited Therapy

The following treatments are prohibited for all subjects during the study:

- Phototherapy (PUVA and/or UVB): UVB within 2 weeks of the baseline visit and PUVA phototherapy within 4 weeks of the baseline visit;
- Other systemic therapies for Ps, PsA and nail Ps (excluding MTX), including cyclosporine, retinoids and fumaric acid esters, within 4 weeks of the baseline visit;
- Oral or injectable corticosteroids and new prescription topical therapies, including shampoos with corticosteroids or changes in the concentration of current prescription topical therapies (including corticosteroids) that are being used, within 2 weeks of the baseline visit. However, subjects may continue using previously prescribed topical therapies (including corticosteroids) during the study. All

biologic therapies that would have a potential impact on Ps including but not limited to the following:

- Remicade® (infliximab)
- Enbrel® (etanercept)
- Tysabri® (natalizumab)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Actemra (tocilizumab)
- Cimzia® (certolizumab)
- Benlysta® (belimumab)
- Simponi® (golimumab)
- Orencia® (abatacept)
- Stelara® (ustekinumab)

- Live vaccines (during the study and for 70 days after the last dose of study drugs) (including but not limited to the following: monovalent live attenuated influenza A (H1N1) [intranasal], seasonal trivalent live attenuated influenza (intranasal), herpes zoster, rotavirus, varicella (chicken pox), measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV), oral polio vaccine (OPV), smallpox, yellow fever, Bacillus Calmette-Guerin (BCG) or typhoid);

- Any investigational agents.

Contact the AbbVie Medical Monitor identified in Section 6.1.5 if there are any questions regarding prohibited therapy (ies).

#### 5.2.3.4 Rescue Therapy

There are no rescue therapy protocols for this study.

### 5.2.4 Contraception Recommendations and Pregnancy Testing

For female subjects:

- If female, subject must be either 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.

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
- Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 150 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 3 month prior to Study Day 1.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 3 month prior to Study Day 1.
  - Bilateral tubal occlusion/ligation.
  - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence] e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

For male subjects:

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 150 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 150 days after the last dose of study drug.

## 5.3 Efficacy, Pharmacokinetic and Safety Assessments/Variables

### 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Safety data will be collected in the form of AEs, vital signs, physical examination results, and clinical laboratory tests throughout the treatment period. AEs will be collected for all subjects up to 70 days after the last study drug injection of ADA, or until the subject begins use of commercial ADA, whichever comes first.

The visit window for all scheduled study visits is ± 3 days for all visits following the Baseline study visit. If a subject has an out of window visit, the next visit should occur as originally scheduled based on the first date of study drug administration (Baseline visit).

All study data will be recorded in the source documents and on the appropriate eCRF. Study procedures will be performed as summarized in the visit schedule presented in Table 1.

**Table 1. Study Activities**

| Activity | Pre-screening ( >Day -35) | Screening (Day -35 to – 3) | Day –0/ Baseline[t] | Week 8 +/- 3 days | Week 16 +/- 3 days | Week 24/ET +/- 3 days | 70-Day F/U[a] | Unsch. Visit[b] |
|---|---|---|---|---|---|---|---|---|
| Satisfaction questionnaire-Investigator | | X | | X | X | X | | |
| Informed Consent | X[c] | X | | | | | | |
| Inclusion/Exclusion criteria | | X | X | | | | | |
| Medical and Surgical History | | X | X | | | | | |
| Alcohol and Nicotine Use | | X | | | | | | |
| Physical Exam[d] | | X | X | X | X | X | | X |
| 12-Lead ECG | | X[e] | | | | | | |
| Chest X-Ray | | X[f] | | | | | | |
| TB testing | | X[g, h] | | | | | | |
| Vital Signs/Weight/Height[i, j] | | X | X | X | X | X | | X[k] |
| Concomitant medication | | X | X | X | X | X | | |
| Hematology | | X | X[l] | X | X | X | | |
| Chemistry | | X | X[l] | X | X | X | | |
| Urinalysis | | X | X[l] | X | X | X | | |
| HBV and HCV screening | | X | | | | | | |
| HIV | | X[m] | | | | | | |
| Pregnancy Test | | X[n] | X[o] | X[o] | X[o] | X[o] | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ANA/dsDNA | | X | | | | | | |
| Serum samples for PK (ADA) | | | X | X | X | X | | |
| Hs-CRP | | | X | | | X | | |
| ADA wash-out (for subjects on ADA 40 mg once weekly)[p] | X | | | | | | | |
| Satisfaction questionnaire-Subject | | X | | X | X | X | | |
| PASI evaluation | | X | X | X | X | X | | |
| Physicians Global Assessment of Ps (PGA) | | X | X | X | X | X | | |
| DLQI | | X | X | X | X | X | | |
| Body Surface Area (BSA) | | X | X | X | X | X | | |
| Monitor Adverse Events[q, r] | | | X | X | X | X | X | |
| Dispense Study Drugs[s] | | | X | X | X | | | |
| Perform drug accountability | | | | X | X | X | | |
| Subject dosing diary dispensing | | | X | | | | | |
| Subject dosing diary review | | | | X | X | X | | |

a. Subjects will be contacted approximately 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects that continue on ADA therapy after the end of study participation.

b. If an unscheduled visit falls within 7 days of the next planned visit, and if all the required procedures of the planned visit are performed, the unscheduled visit accounts for the planned visit. The CRF for the planned visit should be completed.

c. Only for subjects requiring an ADA washout period.

d. A full physical examination should be performed at Screening, Baseline and the Week 24 visits. A symptom directed physical examination should be performed at all other visits if, in the opinion of the Investigator, it is warranted

e. ECG will not be required if normal ECG has been taken within 90 days of the Screening visit and documentation is available

f. A chest X-ray will not be required if the subject had a previous normal X-ray within 90 days prior to Screening (and films with required report results are available)

g. PPD or an IGRA test (QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) will be performed and assessed locally, when available, at Screening

h. If a subject had a negative PPD or IGRA test within 90 days prior to Screening, and all protocol required documentation is available, this test does not need to be repeated. Subjects who have had an ulcerating reaction to tuberculin skin or IGRA test in the past should not be re-exposed and should not be tested. Those subjects with a positive PPD history do not need to be tested, but must have had a documented full course of prophylactic treatment or must begin and have taken at least two weeks of prophylactic treatment prior to first study drug administration. Prophylaxis may also be initiated if a subject has significant exposure to a patient with active TB

i. Vital sign determinations include sitting blood pressure, heart rate, respiratory rate, and body temperature

j. Height will only be measured at the Baseline visit

k. Only the vital signs are required at an unscheduled visit

l. Laboratory assessments will only need to be repeated at Baseline if the time between Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test

m. Documentation from the physician that the subjects are not known to be HIV positive, or at risk for HIV risk factors, will be sufficient. HIV testing is not required unless, in the opinion of the Investigator, it is warranted. A subject will not be eligible for study participation if documentation indicates a positive HIV infection. AbbVie will not receive results from any HIV testing and will not be made aware of any positive result

n. All females of childbearing potential will have a serum pregnancy test at Screening

o. All females of childbearing potential will have a urine sample performed locally at Baseline prior to study enrollment, at week 8, 16 and study discontinuation/completion. 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

p. Wash out procedure for subjects on 40 mg once weekly; these subjects should be started on ADA 40 mg eow for at least 8 weeks prior to study enrollment

q. All AEs reported from the time of study drug administration until 70 days following last study drug injection will be collected

r. SAEs will be collected from the time the subject signed the study-specific informed consent form until 70 days following last study drug injection

s. Last dose of MTX will be taken on Week 23 and last dose of ADA will be taken at Week 22. Drugs will not be dispensed at Week 24

t. Subjects should continue to receive adalimumab every other week during the screening period (if applicable) and the Baseline visit should coincide with the next planned dose of ADA.

#### 5.3.1.1 Study Procedures

The study procedures as specified in Table 1 are discussed in detail in this section. All study data are to be recorded in the source documents and transcribed onto the appropriate eCRF.

Subjects that initially screen fail for the study may be permitted to re-screen only one time following re-consent. All screening procedures with the possible exceptions noted below will be repeated. The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the assessment of a PPD test or a QuantiFERON-TB Gold test ,Chest x-ray and ECG, these tests will not be required to be repeated for re-screening provided the conditions noted in Section 5.2 are met and no more than 3 months (90 days) have passed. As appropriate, sites are encouraged to contact the AbbVie Medical Monitor to confirm if subjects should or should not be re-screened.

**Informed Consent**

A signed informed consent will be obtained from the subject or their legally authorized representative before any study-related procedures are undertaken (including completion of the satisfaction questionnaire), or before any medications are withheld from the subject in order to participate in this study. Details about how informed consent will be obtained and documented are provided in Section 9.3.

**Inclusion/Exclusion Criteria**

Subjects will be eligible for study enrollment if he/she meets all inclusion criteria and none of the exclusion criteria at the Screening and Baseline visits.

**Medical and Surgical History**

A complete non-Ps related medical and surgical history, as well as a history of alcohol use, will be obtained from each subject during the Screening Visit. Whenever possible, the subject's medical chart will be obtained from the family physician or the referring physician. In addition, a list of each subject's specific Ps related medical and surgical history should be recorded at Screening. An updated medical history will be obtained prior to study drug administration at Baseline and updated as necessary throughout the study.

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

**Concomitant Medication**

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

**Physical Examination**

A full physical exam will be performed at the designated study visits as described in Table 1. A symptom-directed physical examination should be performed at all visits if, in the opinion of the Investigator, it is warranted by the subject's AE status or upon review of symptoms. Physical exam abnormalities noted by the Investigator at Baseline prior to the first dose of study medication should be recorded in the subject's medical history. Abnormalities noted after the Baseline visit and first dose of the study medications should be evaluated and documented by the Investigator as to whether or not these are AEs. All physical examination findings, whether related to an AE or part of each subject's medical history, should be captured on the appropriate eCRF page.

**12-Lead Electrocardiogram (ECG)**

A resting 12-lead ECG will be performed at the screening visit. A qualified physician will interpret, sign, and date each ECG. Any clinically significant findings will be documented

in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible Clinical Research Associate (CRA) and kept with the subject's source documentation 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 Medical Monitor 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).

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 Principal 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 Principal Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB.

A PPD skin test (alternatively, also known as tuberculin skin test) must be placed or a QuantiFERON-TB Gold 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 test or QuantiFERON-TB Gold test within 90 days prior to Screening, and all protocol required documentation is available, the test

does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases must be discussed with the Medical Monitor

**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." A two-step test may be performed if required 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 tuberculin 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.

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

If PPD or QuantiFERON-TB Gold testis 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 Centers 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) before enrolling into the study.

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 QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test test will supersede the result of the PPD test. If the QuantiFERON-TB Gold test 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.

Under no circumstances can a subject with a positive PPD result and no prior history of treatment for active or latent TB be allowed into this trial.

**Vital Signs/Weight/Height**

Vital sign determinations of sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit. Weight will be obtained at each visit. Subject's height will be measured at the Baseline visit only. All measurements will be recorded in metric units where applicable.

**Satisfaction with Treatment Evaluation**

Satisfaction with treatment will be assessed using a questionnaire similar to one developed by Christophers et al (28) for quantifying physician and Ps subject satisfaction with biologic therapy. In this study, dermatologists and subjects were surveyed regarding their satisfaction with therapy using the following questions:

Dermatologist survey question: Overall, at this point in time, how satisfied are you with the Ps control provided by the subject's current treatment regimen?

Subject survey question: Overall, how satisfied are you with your current treatment for Ps?

The same questions will be used in the present study. The response choices provided will be:

- Completely dissatisfied
- Moderately dissatisfied
- Slightly satisfied
- Highly satisfied
- Completely satisfied

Within the context of the study, Investigators indicating complete or moderate dissatisfaction with treatment will be combined to indicate subjects eligible for the study during screening (i.e., subjects with a sub-optimal response to ADA). Satisfaction with therapy will be defined by the combination of highly or completely satisfied responses. The questionnaires will be administered during screening and after 8, 16 and 24 weeks of ADA/MTX. Additional details of the questionnaire structure are provided in Appendix C.

**Psoriasis Area and Severity Index (PASI) Evaluation**

A qualified physician or qualified designee will perform the PASI assessment at the designated study visits identified in Table 1. The site will make every attempt to have the same investigator or qualified designee perform this assessment throughout the study for

each subject. All raw data used to determine the PASI will be documented on a worksheet and transcribed onto the appropriate eCRF. The PASI worksheets will be kept by the site in the subject's source documentation. Information and instructions on the calculation of the PASI score are provided in Appendix D. AbbVie will provide training for any Investigator or qualified designee who has not previously performed the PASI assessment.

**Physician's Global Assessment (PGA) of Ps**

The PGA is a 6-point scale used to measure the severity of a subject's Ps. The Investigator or qualified designee will perform a PGA of Ps (Appendix E) at the designated study visits identified in Table 1. The site will make every attempt to have the same investigator or qualified designee perform this assessment throughout the study for each subject.

**Dermatology Life Quality Index (DLQI)[30]**

Subjects will complete the DLQI at Baseline and Weeks 8, 16 and 24. Details of the DLQI are provided in Appendix F.

**Body Surface Area Affected by Ps**

Body surface area affected by Ps will be measured at the designated study visits indicated in Table 1. The subject's hand should be used 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%. Measurement of the total area of involvement by the Investigator or qualified designee is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved. The site will make every attempt to have the same investigator or qualified designee perform this assessment throughout the study for each subject.

**Clinical Laboratory Tests**

For this study, Investigators will use a central laboratory for all laboratory tests and should follow the instructions regarding processing and shipment of samples provided by the laboratory and AbbVie.

Blood and urine samples will be obtained for clinical laboratory tests. When blood draws are performed as part of a clinic visit, the draws should be performed after completion of questionnaires and vital sign measurement, and before study drug administration. Blood specimens for hematology and chemistry will be obtained at Screening, Baseline and Weeks 8, 16 and 24 study visits. Blood specimens will also be drawn at the same visits for analysis of ADA serum concentrations; in this case it is particularly important that blood samples be drawn before administration of ADA.

Urine samples will be obtained for urinalysis testing at Screening, Baseline, and Weeks 8, 16, and 24. The central laboratory should perform a macroscopic urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses

defined as leukocytes, nitrite, protein, ketones or blood greater than negative, or glucose greater than normal should be followed up with a microscopic analysis at the central laboratory.

All required clinical laboratory tests are outlined in Table 2.

**Table 2. Clinical Laboratory Tests**

| Chemistry | Hematology | Urinalysis | Quantiferon TB Gold | Other |
|---|---|---|---|---|
| Albumin<br>Alkaline Phosphatase<br>ALT<br>AST<br>Calcium<br>Cholesterol<br>Creatinine, Enzymatic<br>Glucose, Random, Serum<br>Phosphate<br>Potassium<br>Sodium<br>Total Bilirubin<br>Total Protein<br>Triglycerides<br>Urea (BUN)<br>Uric Acid | Basophils<br>Eosinophils<br>HCT<br>HGB<br>Lymphocytes<br>Monocytes<br>Neutrophils<br>Platelets<br>RBC<br>WBC | Blood<br>Glucose, Urine<br>Ketones<br>Leukocytes<br>Nitrite<br>pH<br>Protein, Urine<br>Specific Gravity<br>Urine Microscopic | Quantiferon Mit. minus NIL<br>Quantiferon NIL<br>Quantiferon TB Gold<br>Quantiferon TB minus NIL | ANA Pattern<br>Anti-ds DNA<br>Antinuclear Antibody<br>C-Reactive Protein, HS<br>HBV DNA PCR Taqman<br>HCG, Quantitative<br>Hep B Core Ab<br>Hep B Surface Ab<br>Hep B Surface Ag<br>HIV 1 & 2 EIA Ab Screen<br>Hep C Ab Screen |

**Hepatitis B and Hepatitis C Testing**

All subjects will be tested for the presence of the Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) at Screening. A positive result for Hepatitis C and/or 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. Also, subjects showing a positive HBc Ab Total test, indicating a previous Hep B exposure, will be excluded due to risk of reactivation or worsening of hepatitis B with MTX.

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 (+)

**Human Immunodeficiency Virus (HIV) Testing**

Documentation from the physician that subjects are not known to be HIV positive or do not have a high risk for HIV infection will be sufficient for this study. Details of this documentation should be recorded in the eCRF. However, in the absence of such documentation subjects should be tested for antibodies to HIV at Screening, and test results documented. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from any testing and will not be made aware of any positive result.

**Immunologic Laboratory Testing**

High sensitivity C-reactive protein (hs-CRP), antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) assessments will be performed in a central laboratory as indicated in Table 1.

**Pregnancy Tests**

A serum pregnancy test will be performed at the Screening visit on all female subjects of childbearing potential. At the Baseline visit, as well as at week 8, 16 and 24, subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a serum pregnancy test will be

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

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined above) at Screening do not require pregnancy testing.

**Pharmacokinetic (PK)/serum ADA Sampling**

Blood collection will be performed prior to medication dosing according to the visit schedule outlined in Table 1. Refer to Section 5.3.2 for sample collection and handling instructions.

**Subject Enrollment**

All Screening laboratory results must be reviewed, signed and dated by the Principal Investigator or Sub-Investigator at each site prior to the Baseline visit. Subjects will not be enrolled into the study if laboratory or other Screening result abnormalities are deemed clinically significant by the Principal Investigator or sub-Investigator.

Subjects should continue to receive adalimumab every other week during the screening period (if applicable) and the Baseline visit should coincide with the next planned dose of ADA.

**Adverse Events**

AEs will be assessed at every study visit from the first dose of study medication through to Week 24 study visit, and during the 70-day safety phone call after the last dose of ADA (or until the subject begins use of commercially available ADA, whichever comes first). In addition, all serious adverse events (SAEs) will be captured from the time the subject signs the Informed Consent Form through study completion or Premature Discontinuation and at the 70-day safety follow-up. Any new AEs/SAEs reported during the 70-day follow-up period should be submitted to AbbVie. The 70-day safety follow-up phone call

will be recorded in source documents only and confirmation of the contact will be faxed to AbbVie (Refer to Section 5.4.1 and Appendix G for additional information).

**ADA Wash-Out**

This is restricted to potentially eligible subjects who on identification by the Investigator, are receiving ADA at a dose of 40 mg once weekly. These subjects should be initiated on ADA 40 mg eow for at least 8 weeks prior to screening. Documentation on date of initiation of wash-out and confirmation of all additional inclusion criteria must be recorded in the eCRF.

**Study Medication Dispensing**

ADA and MTX will be dispensed to subjects beginning at Baseline, at Weeks 8 and 16; no study medications will be dispensed at Week 24. Refer to Section 5.5 for additional information.

**Subject Dosing Diary**

All subjects will be given a subject dosing diary to record all ADA injection dates and times and MTX weekly dosing schedules. Subjects should also record missed ADA and MTX doses in their dosing diary.

**Unscheduled Visit**

If required, an unscheduled visit can be performed according to the visit schedule outlined in Table 1. If the unscheduled visit falls within 7 days of the next planned visit, and if all the required procedures of the planned visit are performed, the unscheduled visit accounts for the planned visit. The CRF for the planned visit should be completed.

### 5.3.2 Drug Concentration Measurements

#### 5.3.2.1 Collection of Samples for Analysis

Blood samples for the measurement of serum ADA concentrations will be collected at Baseline, Weeks 8, 16 and 24. Blood samples should be drawn prior to administration of both ADA and MTX.

#### 5.3.2.2 Handling/Processing of Samples

The blood samples for PK measurements will be centrifuged within 60 minutes of collection to separate the serum. The serum samples will be transferred using sterile plastic pipettes into screw-capped polypropylene vials labeled with the study drug number, protocol number, subject number, and study week. The serum samples will be frozen within 2 hours after collection and will remain frozen in a –20°C or colder freezer after collection until shipment. Sites that do not have access to a –20°C or colder freezer must ship the samples the day they are collected.

Sample collection and handling instructions will be provided by the central laboratory to the investigative sites.

#### 5.3.2.3 Disposition of Samples

The frozen serum samples will be packed in dry ice (pellet form) sufficient to last 3 days during transport. Samples will be shipped pursuant to instructions from the central laboratory. An inventory of the samples will be included in the package for shipment. The investigative site will need to identify a dry ice source and will be responsible for purchasing the necessary amount of dry ice for shipment of frozen samples. Shipping kits for the samples will be provided by the central laboratory.

Arrangements will be made with the central laboratory for the transfer of samples.

#### 5.3.2.4 Measurement Methods

Serum concentrations of ADA will be determined using a validated assay method. All methods will be performed under the supervision of the Drug Analysis Department at AbbVie.

### 5.3.3 Efficacy Variables

#### 5.3.3.1 Primary Variable(s)

The primary efficacy endpoints will be:

- Based on Investigator assessment, the proportion of subjects (primary and secondary sub-optimal responders at baseline) achieving a satisfactory response to ADA + MTX treatment after 16 weeks (satisfactory response defined as highly or completely satisfied with subject's therapy based on responses to the satisfaction questionnaire);
- Based on subject self-assessment, the proportion of subjects (primary and secondary sub-optimal responders at baseline) achieving a satisfactory response to ADA + MTX treatment after 16 weeks (satisfactory response defined as highly or completely satisfied with therapy based on responses to the satisfaction questionnaire).

#### 5.3.3.2 Secondary Variable(s)

Secondary efficacy endpoints will include:

- The proportion of subjects (primary and secondary sub-optimal responders at baseline) achieving 50%, 75%, 90% and 100% reductions in PASI at 8, 16 and 24 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- The proportion of primary sub-optimal responders achieving 50%, 75%, 90% and 100% reductions in PASI at 8, 16 and 24 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);

- The proportion of secondary sub-optimal responders achieving 50%, 75%, 90% and 100% reductions in PASI at 8, 16 and 24 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- The proportion of subjects on ADA 40 mg eow prior to baseline or 40 mg once weekly prior to wash-out achieving 50%, 75%, 90% and 100% reductions in PASI 16 weeks after initiation of ADA + MTX (change in PASI based on score at initiation of ADA + MTX therapy);
- Proportion of primary and secondary sub-optimal responders achieving a clinical response defined as a PGA of "Clear" or "Minimal" at 8, 16 and 24 weeks after initiation of ADA + MTX;
- DLQI scores at baseline (at initiation of ADA + MTX) and at weeks 8, 16 and 24;
- Change and percent change in DLQI from baseline to weeks 8, 16 and 24;
- Proportion of subjects with each of the five categories of satisfaction with treatment at baseline (at initiation of ADA + MTX) and at weeks 8, 16 and 24 (subject self-assessment and Investigator assessment using the satisfaction questionnaires);
- Proportion of primary and secondary sub-optimal responders achieving a DLQI score of 0 or 1 at 8, 16 and 24 weeks after initiation of ADA + MTX;
- Serum levels of ADA in subjects at baseline (at initiation of ADA + MTX) and at weeks 8, 16 and 24.

### 5.3.4 Safety Variables

Safety analyses will be performed on all subjects who receive at least one dose of ADA and MTX. Incidence of AEs and changes in vital signs, physical examination results, and clinical laboratory tests (hematology, chemistry and urinalysis) will be assessed.

### 5.3.5 Pharmacokinetic Variables

ADA trough serum concentrations will be summarized for subjects at each time point using descriptive statistics. Data will be provided for all subjects and for subjects differentiated on the basis of whether they were primary or secondary sub-optimal responders to prior ADA therapy at Baseline.

## 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 AE, safety concerns or failure to comply with the protocol.

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

- Clinically significant abnormal laboratory result(s) or AEs, as determined by the Investigator in consultation with the AbbVie Study-Designated Physician.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drugs, when continuation of the study drugs would place the subject at risk, as determined by the AbbVie Medical Monitor (see Section 7.0).
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Study-Designated Physician.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- Subject has dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie Medical Monitor and the Investigator.

If, during the course of study drugs administration, the subject prematurely discontinues either ADA or MTX, the procedures outlined for the Termination Visit must be completed within 2 weeks of the last dose of either 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 ADA or MTX, the subject will be treated in accordance with the Investigator's best clinical judgment.

A final phone call will be made to the subject 70 days after the last dose of ADA to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs unless not required, as outlined in Section 5.1.

In the case of subjects who prematurely discontinue ADA or MTX, all attempts must be made to arrange a Termination Visit or to contact subjects by telephone. This visit should be used to determine the date of the last dose of study drugs and the primary reason for premature discontinuation and assessment of AEs. Any necessary laboratory tests and physical examinations should also be carried out. The information will be recorded on the appropriate eCRF page.

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

ADA will be provided as a sterile, preservative-free solution for injection in 1 mL pre-filled pens containing ADA 40 mg/0.8 mL. Subjects will be advised to self-administer ADA eow starting at the Baseline visit (Week 0) through Week 24; last injection will be at Week 22. Subjects will not receive a loading dose of 80 mg ADA at Baseline since all subjects should already be receiving a fixed ADA dose of 40 mg eow. Subjects will be dispensed 2 ADA kits at baseline (4 pens with 40 mg ADA pens); subjects will inject one pen at the site at Baseline and remaining 3 pens will be taken home for eow dosing at Weeks 2, 4 and 6. Subjects will return to the site at Week 8 where they will receive another 2 ADA kits; this cycle will repeat at Week 16.

MTX will be provided as 2.5 mg tablets for oral administration. Dose is up to the discretion of the Investigator but recommended dose should be between 10 and 25 mg/week, beginning at Week 0 through Week 23. The minimum initial dose of MTX should be 10 mg/week. Subjects will be advised by the Investigator as to the appropriate dose and the number of pills required to achieve this dose. If dose is > 10 mg/week, dose should be split (divided into two doses, administered on the same day). MTX dose can be increased at any time over the study period, based on the clinical judgment of the Investigator. Subjects will receive sufficient MTX tablets at Baseline for dosing until Week 8 Visit; additional MTX tablets will be provided at Week 8 and 16 Visits. All MTX dose adjustments, and the reasons for the adjustment, should be recorded in the eCRF. Allocation of MTX tablets will be adjusted at site visits to reflect any dosing changes.

All subjects will also receive the non-investigational medicinal product oral folic acid as a dietary supplement since MTX acts as a folic acid antagonist. The folic acid tablets will be provided by the Investigator at a dose of 1.0 mg per day. The required folic acid dose must be taken every day of the week except on the day when MTX is taken. The Investigator will provide specific instructions on the number of folic acid tablets each subject should take. In the event a subject forgets to take the tablets or takes more or less

than is required, they will be instructed to contact the Investigator for guidance. Unused folic acid tablets should be returned to the investigative site.

Each site will be responsible for tracking the lot numbers and expiration dates for all non-investigational medicinal products (e.g. folic acid) that are dispensed.

### 5.5.2 Identity of Investigational Product(s)

The individual study drug information is presented in Table 3.

**Table 3: Identity of Investigational Products**

| Drug | Mode of administration | Formulation | Manufacturer |
|---|---|---|---|
| Adalimumab | Subcutaneous injection | 40 mg/0.8 mL solution for injection<br><br>Adalimumab/citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium citrate, sodium chloride, sodium hydroxide (added as necessary to adjust pH), and water for injection | AbbVie |
| Methotrexate | Oral | 2.5 mg tablets<br><br>Methotrexate/corn starch, lactose, magnesium stearate | Hospira Health Care Corporation or equivalent |

#### 5.5.2.1 Packaging and Labeling

ADA will be provided as a solution for injection (Table 3), packaged as a prefilled pen containing 40mg ADA/0.8 mL with two pens in a carton. MTX 2.5 mg tablets will be supplied in bottles containing 100 tablets per bottle. Supplies will be labeled in an open-label format. Each kit label will include all information as required by local regulations. All blank spaces on the label will be filled in by site staff prior to dispensing to the

subject. The labels must remain affixed to the primary and potential secondary packaging material at all times.

Each ADA carton and MTX bottle will contain a unique number that is assigned to a subject via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The type and number of kits dispensed will be managed by the IVRS/IWRS.

#### 5.5.2.2 Storage and Disposition of Study Drug(s)

ADA pre-filled pens 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.

MTX should be stored protected from light and moisture at 15°C to 25°C/59° to 77°F according to labeled storage conditions.

A storage temperature log is to be maintained to document proper storage conditions. The refrigerated temperature must be recorded on a temperature log to record proper function. Malfunctions or any temperature excursion must be reported to the Sponsor immediately. Study medication should be quarantined and not dispensed until AbbVie GPRD or AbbVie Temperature Excursion Management System (ATEMS) deems the medication as acceptable. All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie.

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

### 5.5.3 Method of Assigning Subjects to Treatment Groups

There is no randomization in this study. All subjects will receive the same therapy. All subjects will be assigned a subject number by the IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS/IWRS will be provided to each site.

### 5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study medication as outlined in Section 5.5.1.

The kit number(s) to be dispensed, both for ADA and MTX, will be assigned by the IVRS/IWRS. Each ADA carton and MTX bottle will contain a unique number that is assigned to a subject via IVRS/IWRS. The number of kits dispensed will be managed by the IVRS/IWRS. On dosing days that occur on study visit days, subjects will administer ADA drug injection in the office under guidance of study site personnel after all specified study tests and procedures have been completed. Although subjects should be familiar with sterile subcutaneous injection technique, qualified study site personnel should directly observe subject self-injection at the time of all scheduled visits to ensure that it is carried out correctly. Site personnel observation of the subject's self-injection technique is of particular importance during the Baseline Visit. This supervision will serve as a confirmation of the use of safe and appropriate drug injection techniques and to answer any questions related to drug administration. ADA doses that do not occur on study visit days should be administered to subject by himself/herself, or by a designee (friend, family member or health care professional) throughout the study. For MTX, subjects should be instructed to bring their drug with them on study visit days that coincide with subject's MTX dosing schedule so that MTX can be taken in the office. Again, qualified study site personnel should observe oral MTX dosing, particularly to ensure that the correct number of tablets are taken for the prescribed MTX dose.

Each subject's dosing schedule should be closely monitored by the site at each study visit by careful review of the subject's dosing diary. This will ensure that all subjects enrolled into the study maintain their original ADA dosing schedule beginning with the first dose of study medication (Baseline/Day 0). Doses of ADA should be taken on the same "scheduled dosing day" of each appropriate dosing week. Dosing schedule for MTX should also be closely reviewed to ensure that drug is taken at the required dose per week and, if the weekly drug dose is split (i.e. > 10 mg/week), that the dose is taken on the same day in two equal doses. In addition, dosing diaries should be reviewed to ensure that the subject has adjusted dosing to reflect any study-related MTX dose increases.

If a subject should forget to administer the ADA injection on their regularly scheduled dosing date, they should take the forgotten injection as soon as they remember the dose was missed up to the day before their next scheduled dose. The subject should not administer two ADA injections on the same day. If a subject should forget to take an MTX dose, they should take the forgotten dose as soon as they remember the dose was missed up to 3 days before their next scheduled dose. Subjects should be encouraged to record incorrect or missed ADA and MTX doses in their dosing diary. 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.

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

The folic acid tablets will be provided by the Investigator at a dose of 1.0 mg per day. The required folic acid dose must be taken every day of the week except on the day when the MTX is taken. The Investigator will provide specific instructions on the number of folic acid tablets each subject should take.

### 5.5.5 Blinding

There is no blinding in this study. All subjects will receive the same treatment, except for possible variation in the dose of MTX which will not be blinded.

### 5.5.6 Treatment Compliance

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

The subject or their qualified designee will administer all doses of ADA and MTX. 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 ADA and MTX treatment regimens, the subject will be given a subject dosing diary to record all ADA injection dates and times and MTX weekly dosing schedules. Compliance information will be documented on the appropriate eCRF. Subjects will be counseled on missed doses of ADA and MTX. If the subject does not return the dosing diary, unused ADA or MTX, empty Investigational Product (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 study medication. The subject should be instructed to return all items at the next scheduled visit or sooner if possible. The information should be documented on the source documents as per "best recollection" and when possible, re-verified when the dosing diary is returned before completing the applicable eCRF page.

### 5.5.7 Drug Accountability

The Investigator or designee will verify that drug supplies are received intact, at the appropriate temperature and in the correct amounts from the drug depot. 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 and by registering the arrival of medication through the IVRS/IWRS. The original POR Note and the IVRS/IWRS confirmation will be kept in the site files as a record of what was received.

In addition, an IVRS/IWRS will be used to document investigational product accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number and the identification of person dispensing the drug. All empty IP boxes/bottles and used pre-filled pens will be inventoried by the site and verified by the CRA. Each subject will be given their own sharps disposal container to store used pens. Empty IP boxes/bottles and Sharps containers should be returned by the subject at

each visit for accountability and compliance purposes and new containers issued as necessary. Empty boxes/bottles and returned Sharps containers will be retained until the CRA is on site to confirm the returned medication. CRAs and site staff will complete study medication accountability via source documents, subject dosing diaries and empty IP boxes/bottles and by visually inspecting the pens in the Sharps container whenever possible. Used Sharps containers should never be opened. Once the CRA has verified drug accountability at the site, the site staff and CRA will document that the used pens have been destroyed, using appropriate biohazard precautions, when appropriate. A copy of the destruction methodology should be maintained at the site's facility. Unused medications should not be destroyed, but will be returned to AbbVie by the CRA once drug accountability has been completed at the site.

Non-investigational medicinal product (standard of care) (e.g., generic name and generic name) must be obtained commercially.

Unused folic acid tablets should be returned to the investigative site and accounted for to assess subject's compliance.

Investigator must agree not to supply study medication to any persons not enrolled in the study.

## 5.6 Discussion and Justification of Study Design

### 5.6.1 Discussion of Study Design and Choice of Control Groups

This is a single arm, open label, longitudinal study designed to assess the impact of addition of oral MTX to ADA therapy in subjects with Ps who are not responding optimally to ADA monotherapy, either as primary or secondary sub-optimal responders. Sub-optimal response in this case means subjects with an unsatisfactory response to treatment based on an Investigator assessment. Subjects must also have a PGA $\geq$ 3 and a PASI of $\geq$ 5 to be eligible for participation in the study. Efficacy is based on the proportion of subjects with a satisfactory response to ADA + MTX therapy, based on subject self-assessment and an assessment by the Investigator; Ps related clinical

outcomes will also be assessed as will the relationship between serum ADA levels and degree of clinical response. There is no control group in this study; instead each subject serves as their own control and outcomes after addition of MTX are compared to similar assessments at Baseline, prior to the addition of MTX to ADA therapy.

### 5.6.2 Appropriateness of Measurements

The most recent Canadian Ps treatment guidelines recognize the importance of the patient's preferences and priorities in treatment decisions (2). This study incorporates, as a primary objective, subject satisfaction with therapy, in order to incorporate this patient-centered approach, and also includes Investigator assessment of satisfaction with treatment response. In addition, the study includes efficacy measurements which are standard for assessing disease activity in subjects with Ps. All clinical and laboratory procedures in this study are standard and generally accepted.

### 5.6.3 Suitability of Subject Population

Adult subjects 18 years of age or older, with a diagnosis of moderate to severe Ps who have been receiving ADA monotherapy for at least 16 weeks and who, in the opinion of the treating Investigator, have a sub-optimal response to treatment (primary sub-optimal responders), or have not maintained an initial positive response (secondary sub-optimal responders) and who meet all inclusion criteria and none of the exclusion criteria, will be enrolled in this study. The inclusion criteria identify a population who could benefit from the addition of MTX to ADA therapy in treatment of Ps, as has been demonstrated in other immune-mediated diseases such as RA where some subjects do not respond optimally to ADA monotherapy (8,26).

### 5.6.4 Selection of Doses in the Study

ADA doses for this study are those indicated in the Canadian Product Monograph for treatment of Ps (9). The MTX dose (10 to 25 mg/week) is within the range recommended for systemic MTX monotherapy in Ps and RA. In addition, a similar MTX dose range added to ADA therapy has been shown to be effective in treatment of RA (26) and

preliminary studies in Ps show that addition of MTX (10 mg/week) to ADA therapy in subjects with insufficient response to ADA alone improves PASI outcomes (27).

# 6.0 Complaints

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

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pen).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1. 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 AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drugs (causality will be assessed for both ADA and MTX), and any action(s) taken. For SAEs considered as having "no reasonable possibility" of being associated with study drugs, the Investigator will provide an “Other” cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AEs 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 AE 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 AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs 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 AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE 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 AE.

#### 6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE.

| | |
|---|---|
| **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 SAEs 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 AE:

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

### 6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug(s) (causality will be assessed for both ADA and MTX):

| | |
|---|---|
| **Reasonable Possibility** | An AE where there is evidence to suggest a causal relationship between the study drug and the AE. |
| **No Reasonable Possibility** | An AE where there is no evidence to suggest a causal relationship between the study drug and the AE. |

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug(s) will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug(s) 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(s) is given, an “Other” cause of event must be provided by the Investigator for the SAE.

### 6.1.4 Adverse Event Collection Period

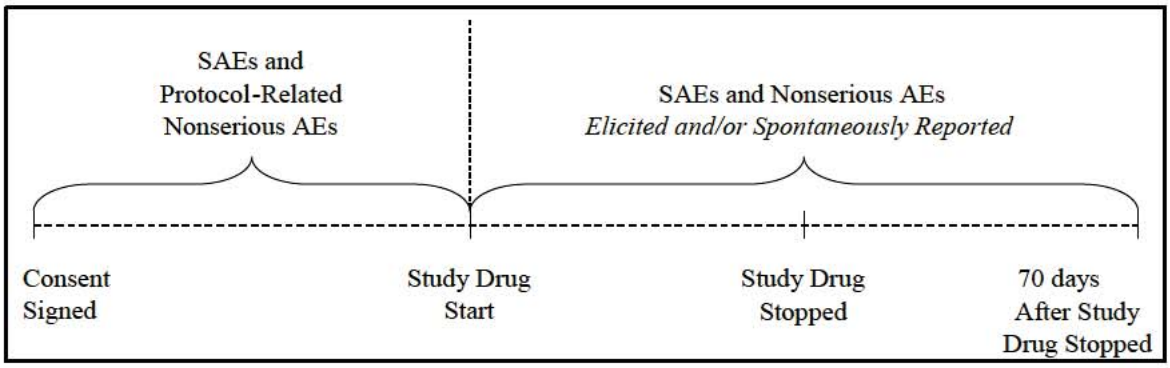
All AE reported from the time of study drugs administration until 70 days following discontinuation of study drugs administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol related

non-serious AEs will be collected from the time the subject signed the study-specific informed consent. AE information will be collected and recorded on the appropriate eCRF.

Subjects will be contacted approximately 70 days following study drug (ADA) discontinuation for an assessment of any new or ongoing AEs, except those subjects that continue on ADA therapy after the end of study participation. These subjects are not required to complete the 70-day follow-up and any new AEs should be reported through the mechanism used for all post-marketing AEs.

AE information will be collected as shown in Figure 2.

**Figure 2. Adverse Event Collection**




### 6.1.5 Adverse Event Reporting

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

AbbVie Clinical Pharmacovigilance Team within 24 hours of the site being made aware of the AE.

**Email:** [redacted]
**FAX to** [redacted]

For safety concerns, contact the Therapeutic Area Safety Team at:

**Immunology Safety Team**

[redacted]

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

**Primary Medical Monitor:**

[redacted]

In emergency situations involving study subjects when the primary Medical Monitor 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 Medical Monitor:

| **Phone:** [redacted] |
|---|

### 6.1.6 Pregnancy

Pregnancy in a study subject or a partner of study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

Pregnancies in study subjects and their partners will be collected from the date of the first dose through 150 days following the last dose of study drug.

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

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

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

### 6.1.7 Toxicity Management

Subjects who develop a new infection while undergoing treatment with ADA and MTX should be monitored closely. Administration of study ADA injections and/or oral MTX should be interrupted if a subject develops an infection requiring intravenous (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 Investigator determines that the

infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessary. Prior to any prohibited medication use, every attempt should be made to contact the AbbVie Medical Monitor for direction on re-introduction of ADA and MTX therapy after prohibited medication administration; however, these communications should not delay the administration of any necessary medication(s), study-prohibited or otherwise, to the subject.

If the subject must undergo elective surgery, the study ADA injections and oral MTX must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study ADA injections and oral MTX must be interrupted at the time of the surgery. ADA and oral MTX 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. If any subject needs to skip more than two ADA doses or two weekly doses of MTX (consecutive or intermittent) over the course of the study, even if for the situations described above, further follow-up on the subject's study participation should be discussed with the AbbVie Study designated Physician.

## 6.2 Product Complaint

### 6.2.1 Definition

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

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

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

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

### 6.2.2 Reporting

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

Product Complaints may require return of the product with the alleged complaint condition (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 local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the Principal Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned Clinical Monitor or the following AbbVie Clinical Monitor(s):

**Primary Contact:** **Alternate Contact:**

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

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

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

# 8.0 Statistical Methods and Determination of Sample Size

## 8.1 Statistical and Analytical Plans

The primary objective of the statistical analyses is to determine the proportion of subjects with Ps who have a satisfactory response to ADA + MTX treatment, based on a self-assessment by subjects and an assessment by the treating Investigator. Secondary objectives include an evaluation of the efficacy of ADA + MTX in subjects with Ps and characterization of the possible relationship between serum levels of ADA and efficacy outcomes. The impact of MTX on ADA serum levels will also be assessed by defining the change in serum ADA from baseline following the addition of MTX to therapy. Safety of ADA + MTX will also be assessed.

Complete specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock.

### 8.1.1 Analysis Population

The intent-to-treat (ITT) population will be used in the assessment of treatment satisfaction and in the evaluations of ADA + MTX efficacy. The ITT population is defined as:

- All subjects who received at least one dose of ADA and one dose of MTX.

A per protocol population will not be defined for this qualitative study.

The safety population is defined as all subjects who received at least one dose of ADA and one dose of MTX and will be used to evaluate safety of ADA + MTX.

### 8.1.2 Planned Methods for Statistical Analysis

Point estimates and 95% confidence intervals (CIs) will be provided for the discrete efficacy variables such as the proportion of responders to ADA + MTX. Changes from baseline (in PASI, PGA, DLQI and ADA serum levels) will be estimated using an appropriate estimation from a Mixed Model and statistical tests of change from baseline equal to zero will be carried out at the 0.05 significance level. Descriptive statistics will be provided as appropriate. These include the number of observations, mean, and standard deviation for continuous variables and counts and percentages for discrete variables. The analysis will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

### 8.1.3 Demographics and Baseline Characteristics

Demographic and Baseline characteristics of the study subjects will be summarized using descriptive statistics. Characteristics will be defined for the ITT population and for subjects differentiated on the basis of whether they are primary sub-optimal responders or secondary sub-optimal responders at Baseline.

### 8.1.4 Statistical Analysis of Efficacy

The primary and secondary efficacy analyses will be conducted on the ITT population. The primary efficacy analyses will also be conducted for the following sub-populations:

- Subjects defined as primary sub-optimal responders at baseline, based on Investigator assessment;
- Subjects defined as secondary sub-optimal responders at baseline, based on Investigator assessment.

For the primary and secondary efficacy analyses, sub-optimal responder imputation (imputing missing satisfaction data as "dissatisfied") will be used. In the event that greater than 5% of the satisfaction data are missing, the following will be carried out to impute the missing data in sensitivity analyses:

- Last observation carried forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit within the particular period for efficacy measures assessed, to impute missing data at later visits;

Additional exploratory efficacy outcomes will be analyzed using available data at each assessment point and changes over time for PASI, PGA and DLQI scores will be estimated using a Mixed Model. Exploratory analysis to determine associations between ADA serum levels and PASI, PGA and DLQI scores will also be carried out. This could be accomplished using a regression analysis with ADA serum level and visit as explanatory variables and either PASI, PGA or DLQI as response variables and controlling for within subject measurements. To determine the form of the regression model, the exploratory analyses could be carried out using LOESS Regression or general additive models. Alternatively, subjects could be grouped according to predetermined ranges of PASI, PGA or DLQI and the analysis could concentrate on determining differences in ADA serum levels in these groups.

### 8.1.5 Statistical Analysis of Safety

All AEs, SAEs, and AEs leading to discontinuation will be collected during the study and up to 70 days after the last dose of ADA. Safety analyses will be carried out using the Safety Population. A treatment-emergent AE is defined as an event with onset or worsening after the first dose of study drugs (ADA + MTX) and within 70 days after the last dose of ADA. The number and percent of subjects experiencing treatment-emergent AEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-years) of SAEs, deaths and AEs leading to discontinuation from the study will be provided as well.

### 8.1.6 Interim Analysis

No interim analysis is planned for this study.

## 8.2 Determination of Sample Size

This study should have a 30 month recruitment period where it is anticipated that approximately 200 subjects will be recruited. With this sample size the proportion of responders, defined as the proportion of subjects with a highly or completely satisfied response after 16 weeks of ADA + MTX therapy, based on an Investigator assessment and subject self-assessment, can be estimated within ± 4.9% with 95% confidence when the point estimate is 15%, within ± 6.4% with 95% confidence when the point estimate is 30%, or within ± 6.9% with 95% confidence when the point estimate is 50%. Additional accuracy estimates are provided in the Table below.

**Table 4: Accuracy Estimates with a Sample Size of 200 Subjects**

| Estimated Proportion of Responders | Accuracy Estimate |
|---|---|
| 5% | 3.0% |
| 10% | 4.2% |
| 15% | 4.9% |
| 20% | 5.5% |
| 25% | 6.0% |
| 30% | 6.4% |
| 35% | 6.6% |
| 40% | 6.8% |
| 45% | 6.9% |
| 50% | 6.9% |

**Note: Proportion of responders can be estimated with +/- accuracy with 95% confidence. The size of the 95% Confidence Interval would be 2×Accuracy**

Due to the recent enrollment plan change (enroll 50 patients or as the number of enrollment by 31-Dec-2016), Updated accuracy estimates with a sample size of 50 subjects, about the proportion of subjects with a highly or completely satisfied response after 16 weeks of ADA + MTX therapy based on an Investigator assessment and subject self-assessment, are provided in the table below.

**Table 5: Accuracy Estimates with a Sample Size of 50 Subjects**

| Estimated Proportion of Responders | Accuracy Estimate |
|---|---|
| 5% | 6.0% |
| 10% | 8.3% |
| 15% | 9.9% |
| 20% | 11.1% |
| 25% | 12.0% |
| 30% | 12.7% |
| 35% | 13.2% |
| 40% | 13.6% |
| 45% | 13.8% |
| 50% | 13.9% |

**Note: Proportion of responders can be estimated with +/- accuracy with 95% confidence. The size of the 95% Confidence Interval would be 2×Accuracy**

## 8.3 Statistical Analysis of ADA Serum Levels

ADA serum concentrations will be summarized at each time point using descriptive statistics including number of subjects, number of non-missing observations, mean, median, standard deviation, coefficient of variation (CV), minimum and maximum as appropriate. Mean and median concentration versus time plots will be generated. Data will be assessed for the following subgroups:

- Total recruited subjects;
- Subjects defined as primary sub-optimal responders at baseline, based on Investigator assessment;
- Subjects defined as secondary sub-optimal responders at baseline, based on Investigator assessment

To further characterize the relationship between ADA serum levels and treatment response, subjects will be classified as non-responders (< 50% improvement in PASI from baseline (baseline defined as addition of MTX to ADA therapy); moderate responders (≥ 50% to <75% improvement in PASI from baseline) or good responders (≥ 75%

improvement in PASI from baseline) at 8, 16 and 24 weeks. At each visit, median ADA serum levels will be evaluated by group and compared between groups.

In addition, exploratory analysis to determine possible associations between MTX dose and ADA serum levels will be carried out.

# 9.0 Ethics

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

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

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

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Health Canada. 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, 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 form will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other required signatories. 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. Consent must be obtained before any study-related procedures including completion of the Investigator/subject satisfaction assessment. In addition, consent must be obtained before wash-out procedures are initiated in subjects who are receiving ADA 40 mg once weekly; prior to study enrolment these subjects should be treated with ADA 40 mg eow for at least 8 weeks.

Information regarding subject reimbursement for travel expenses 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.

## 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, completed satisfaction questionnaires, 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.

The following assessments will be completed by the Investigator (or qualified designee) and will be considered source documentation:

- PASI assessment
- PGA assessment
- BSA assessment
- Treatment satisfaction questionnaire

The following assessments will be completed by the subject and will be considered source documentation:

- Treatment satisfaction questionnaire
- DLQI

Once collected, these outcome assessments will be entered by AbbVie or the site into the EDC system and will be available for viewing by site personnel.

The AE eCRF data segments of: alternate etiology, severity, frequency and relationship to ADA + MTX may also be used as source documents and will require Investigator approval on the eCRF as verification of the accuracy of the information.

## 10.2 Case Report Forms

Case report forms (CRFs) 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 changed 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

Prior to the initiation of the study, an Investigator's meeting and/or a study initiation visit will be held with the Investigators, their sub-Investigators and study coordinator(s) and AbbVie personnel and/or their designee. This meeting will include a detailed discussion of the protocol, performance of study procedures, completion of the eCRFs, subject questionnaires, subject dosing diary cards, and specimen collection methods.

The CRA will monitor each site throughout the study and source document verification will be performed.

All data entered in the database will be verified at AbbVie. Any discrepancies will be reviewed. The data will be reviewed and computer logic and manual checks will be created to identify items such as inconsistent study dates. A manual review of selected line listings will also be performed at the end of the study. Queries will be generated in the EDC system. Any necessary corrections will be made to the eCRF and documented via addenda or audit trail. The data from the central laboratory analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

## 12.0 Use of Information

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

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of ADA. This information may be disclosed as deemed necessary by AbbVie to other clinical Investigators, other pharmaceutical companies, to Health Canada and the FDA and to other governmental agencies. For the use of the information derived from this clinical

study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to all source data/documents for trial-related monitoring, audits, IEC/IRB review, and regulatory inspection. This confidential information shall remain sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie.

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.

## 13.0 Completion of the Study

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

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

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

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

## 14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for adalimumab and the product monograph for 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: | Concomitant longitudinal evaluation of adalimumab with methotrexate in the real world: the CLEAR study |
| Protocol Amendment 2 Date: | 22 Apr 2016 |

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

## 15.0 Reference List

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## Appendix A. Responsibilities of the Clinical Investigator

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

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.

2. Personally conducting or supervising the described investigation(s).

3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.

4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.

5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).

6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.

7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.

8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

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

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

## Appendix B. List of Protocol Signatories

ABBVIE CORPORATION

Clinical Study Protocol W14-406

Concomitant longitudinal evaluation of adalimumab with methotrexate in the real world: the CLEAR study (protocol amendment 2 dated 22 April 2016)

Approved by:

[redacted]

## Appendix C. Satisfaction Questionnaire

**Subject #:_____**

**Date: _____**

**Satisfaction Questionnaire – Investigator**

Overall, at this point in time, how satisfied are you with the Ps control provided by the subject's current treatment regimen?

- ❑ Completely dissatisfied
- ❑ Moderately dissatisfied
- ❑ Slightly satisfied
- ❑ Highly satisfied
- ❑ Completely satisfied

**Subject #:_____**

**Date:_____**

**Satisfaction Questionnaire – Subject**

Overall, how satisfied are you with your current treatment for Ps?

- ❑ Completely dissatisfied
- ❑ Moderately dissatisfied
- ❑ Slightly satisfied
- ❑ Highly satisfied
- ❑ Completely satisfied

## Appendix D. Psoriasis Area Severity Index (PASI) Scoring Instructions

**PASI Scoring** [31-32]

Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The table below outlines the characteristics of each category.

| | Erythema[a] | Desquamation | Induration |
|---|---|---|---|
| 0 = none | No redness | No scaling | No elevation over normal skin |
| 1 = slight | Faint redness | Fine scale partially covering lesions | Slight but definite elevation, typically edges indistinct or sloped |
| 2 = moderate | Red coloration | Fine to coarse scale covering most of all of the lesions | Moderate elevation with rough or sloped edges |
| 3 = marked | Very or bright red coloration | Coarse, non-tenacious scale predominates covering most or all of the lesions | Marked elevation typically with hard or sharp edges |
| 4 = very marked | Extreme red coloration; dusky to deep red coloration | Coarse, thick, tenacious scale over most or all lesions; rough surface | Very marked elevation typically with hard sharp edges |

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to < 30%
- 3 = 30% to < 50%
- 4 = 50% to < 70%
- 5 = 70% to < 90%
- 6 = 90% to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10%, 20%, 30%, and 40% of BSA, 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* + Dl)Al

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 degree.

## Appendix E. Physician Global Assessment of Skin (PGA-S)

The Physician's Global Assessment (PGA) is a 6-point scale used to measure the severity of skin disease at the time of the qualified investigator's evaluation of the subject. The degree of overall lesion severity will be evaluated using the following categories:

| | Scaling | Erythema | Induration | Score |
|---|---|---|---|---|
| 0 | No evidence of scaling | No evidence of erythema | No evidence of plaque elevation | Cleared, except for residual discoloration |
| 1 | Occasional fine scale over less than 5% of the lesions | Faint erythema | Minimal plaque elevation | Minimal, majority of lesions have score averaging 1 |
| 2 | Fine scale dominates | Light red coloration | Mild plaque elevation | Mild, majority of lesions have score averaging 2 |
| 3 | Coarse scale dominates | Moderate red coloration | Moderate plaque elevation | Moderate, majority of lesions have score averaging 3 |
| 4 | Thick, non-tenacious scale dominates | Bright red coloration | Marked plaque elevation | Marked, majority of lesions have score averaging 4 |
| 5 | Very thick, tenacious scale predominates | Dusky to deep red coloration | Severe plaque elevation | Severe, majority of lesions have score averaging 5 |

(I + E + S)/3 = Score

From briefing document for Ustekinumab, Ustekinumab FDA Advisory Committee Meeting.

## Appendix F. Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life **OVER THE LAST WEEK**. Please tick √ one box for each question.

| Question | Response | |
|---|---|---|
| 1. Over the last week, how **itchy, sore, painful** or **stinging** has your skin been? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | |
| 2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | |
| 3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 4. Over the last week, how much has your skin influenced the **clothes** you wear? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 5. Over the last week, how much has your skin affected any **social** or **leisure** activities? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 6. Over the last week, how much has your skin made it difficult for you to do any **sport**? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |

| Question | Response | |
|---|---|---|
| 7. Over the last week, has your skin prevented you from **working** or **studying**?<br>If "No," over the last week how much has your skin been a problem at **work** or **studying**? | Yes ☐<br>No ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 9. Over the last week, how much has your skin caused any **sexual difficulties**? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |
| 10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time? | Very much ☐<br>A lot ☐<br>A little ☐<br>Not at all ☐ | Not relevant ☐ |

**Please check you have answered EVERY question. Thank you.**

## Appendix G. 70-Day Follow-Up (Phone Call)

**Study W14-406**
**Day 70 Follow-Up (Phone Call)**

Site Name/Number: _____
Subject Number: _____

**Please contact all Subjects 70 days following last study drug injection (ADA)**

Date of Call/Visit: _____

- ☐ Call not needed as subject is continuing on commercial adalimumab.
- ☐ Lost to Follow-Up (Please check this box if subject was not willing to provide any follow-up information or you were unable to speak to the subject following at least one attempt).
- ☐ No Events Reported
- ☐ AE/SAE Reported

List any Adverse Events (AE) and/or Serious Adverse Events (SAE) that occurred since the subject was last seen in clinic for this study. Please document all adverse events on a 500 AE CRF in the EDC system. (Please report all SAEs to AbbVie within 24 hours of being made aware of the event). **In addition, please note stop dates to any adverse events that were ongoing at the last study visit.**

| | |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

**Please fax this form to AbbVie at** [redacted]

**Appendix H. Adalimumab injection instructions**

# Subject Injection Instructions

# 0.8 mL dose

# (Administered as a single dose Pen or pre-filled syringe)

# Protocol W14-406

## Tables of Contents

## STUDY DRUG DOSING SCHEDULE

During the study, you will receive subcutaneous (SC) injections and you will take methotrexate tablets.

**Methotrexate (MTX):**

MTX will be provided as a 2.5 mg tablets for oral administration. MTX tablets will be taken once a week during the study. Your study doctor will let you know how many pills per week need to be taken.

You will be dispensed a bottle of MTX at the Baseline (Day -0) visit. This bottle will contain sufficient MTX tablets for dosing until the Week 8 visit. The first dose will be taken at the clinic at the Baseline (Day – 0) visit. Your study doctor will let you know how many pills you have to take every week. A new bottle of MTX will be dispensed at the Week 8 and 16 visits. You will continue to take MTX once a week. Your study doctor will let you know what dose needs to be taken every week. The last dose of MTX will be at the Week 23. There is no dose taken at the Week 24 visit.

In the event a MTX dose is missed or an incorrect dose is taken, please contact the clinic for instructions. Please return the bottle with the unused tablets at your next visit (Weeks 8, 16 and 24).

Please remember to complete the dosing diary after each dose is taken and call the clinic if you are having difficulties.

**Adalimumab (ADA) injections:**

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

- Baseline (Day – 0) Visit (the first visit to receive study medication for this study): 1 injection at the clinic.
- Starting at Week 2: 1 injection every other week (EOW) through Week 22. Unless the injection is the same week as a clinic visit, you will receive these injections at home.

You will be dispensed 2 ADA kits at the Baseline (Day – 0) Visit (4 Pens or syringes with 40 mg ADA/ Pen or syringe); 1 Pen/syringe from the first kit will be used for the dose administered at the clinic and the remaining 3 Pens/syringes will be taken at home for every other week dosing at Weeks 2, 4 and 6. At the week 8 Visit, 2 ADA kits will be dispensed; 1 Pen/syringe from the first kit will be used for the dose administered at the site and the 3 remaining Pens/syringes will be taken at home at Weeks 10, 12 and 14. At the Week 16 visit, 2 kits will be dispensed; 1 Pen/syringe from the first kit will be used for the dose administered at the clinic and the remaining 3 Pens/syringes will be taken at home at Weeks 18, 20 and 22. The Week 22 dose is the last dose of injectable study medication. There is no dose taken at Week 24.

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

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

Remember to complete your dosing diary after each injection and to call the clinic if you are having problems administering your study medication.

**Folic Acid (vitamin) Pills:**

The folic acid (vitamin) pills will be provided to you by the clinic. You will take folic acid every day of the week except on the day you take the MTX tablet(s). The clinic staff will provide specific instructions on the number of pills you should take.

In the event you forget to take the pills or takes more or less than is required, please contact the clinic for guidance. At the end of the study or if you discontinue from the study, all unused folic acid pills should be returned to the clinic.

**GENERAL INFORMATION**

- Pens or pre-filled syringes will be labeled "Adalimumab 40mg/0.8mL Solution for Injection".

- Bottles with tablets will be labeled "Methotrexate".

- Store all adalimumab Pens or pre-filled syringes in your refrigerator NOT in the freezer. Should the Pens or syringes accidentally become frozen, call your study doctor's office.

- Store all bottles with Methotrexate tablets at room temperature.

- Store the bottle of folic acid at room temperature.

- Study medication should be taken at about the same time of day, on the same day of the week as directed by your study doctor.

- **USE A NEW PEN/SYRINGE EVERY INJECTION DAY.** There may be medication left in the Pen or syringe. **DO NOT RE-USE.**

- Save all study medications. ***Pens or pre-filled syringes (used and unused) & empty boxes must be returned to the study center at each visit.*** Used Pens or syringes will be disposed of in a sharps container provided to you.

- Call your doctor IMMEDIATELY if you experience any itching, hives, shortness of breath, or any symptom that has you concerned. If you are unable to reach your doctor or if you experience life-threatening symptoms **call**, _____ or proceed to your nearest emergency room.

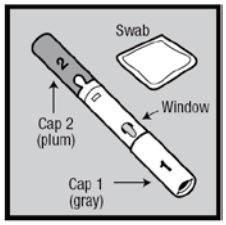
## INJECTION PROCEDURES

### 1. Setting up for an injection

- Find a clean flat surface.
- Do not use if seals on the carton are broken or missing. Contact your study doctor's office if the seals are broken.
- Take one kit with the Pen or pre-filled syringe(s) of adalimumab from the refrigerator. Do not use a Pen or pre-filled syringe that has been frozen or if it has been left in direct sunlight.
- Return any unused Pen(s) or syringe(s) to the refrigerator.
- If you are using the Pen, only remove the caps **immediately** before injection.

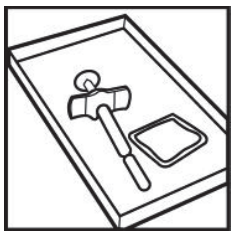
You will need the following items for each dose:

- Study medication in Pen
- Alcohol prep(s)
- Cotton ball or gauze pad(s)




OR

- Study medication in pre-filled syringe
- Alcohol prep(s)
- Cotton ball or gauze pad(s)



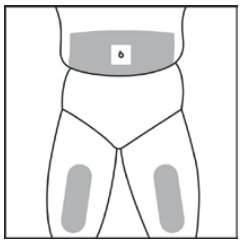
If you do not have all of the items you need to give yourself an injection, call your study physician. Use only the items provided in the box your adalimumab comes in.

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

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

**2. Choosing and preparing an injection site**

- Wash your hands well.
- Choose a site on the front of your thighs or your stomach area (abdomen). If you choose your abdomen, you should avoid the area 5 cm (2 in) around your belly button (navel).
- Choose a different site each time you give yourself an injection. Each new injection should be given at least 2.5 cm (1 in) from a site you used before. Never inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.
- You should try not to inject directly into any raised, thick, red or scaly skin patches or lesions.
- You may find it helpful to keep notes on the location of your injection sites.
- Wipe the site where adalimumab is to be injected with an alcohol prep (Swab), using a circular motion. Do not touch this area again until you are ready to inject.

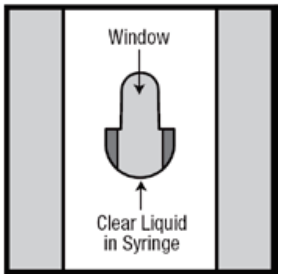


**3. How to prepare your adalimumab dose for injection**

**<u>Pen</u>**

- Hold the Pen with the gray cap pointing up.

- Check the appearance of the solution through the windows on the sides of the Pen to make sure the liquid is clear and colourless.
- Do not use the Pen if the liquid is cloudy or discoloured or has flakes or particles in it.
- Do not use if frozen or if it has been left in direct sunlight.




**Pre-filled Syringe**

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

**4. Injecting Adalimumab**

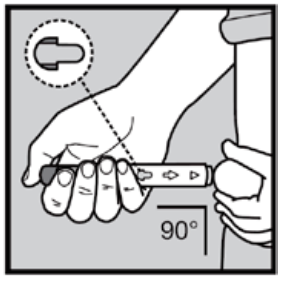
**Pen**

- Only remove the caps **immediately** before injection.
- Hold the gray body of the Pen with one hand.
- Place your hand on the middle of the Pen so that neither the gray cap (Cap 1) nor the plum cap (Cap 2) is covered.
- Hold the Pen with the gray cap (Cap 1) pointing up.
- With your other hand, pull the gray cap (Cap 1) straight off (without twisting) and discard the cap.
- Check that the small needle cover of the syringe has been removed with the cap.
- If a few small drops of liquid come out of the needle, this is okay.
- The white needle sleeve, which covers the needle, will now be exposed. Do not try to touch the needle housed in the barrel.

- **DO NOT RECAP as you may damage the needle**.
- Care should be taken to avoid dropping or crushing the product as it contains a glass syringe.
- Pull the plum safety cap (Cap 2) straight off (without twisting) to expose the plum-coloured activation button. The Pen is now ready to use.

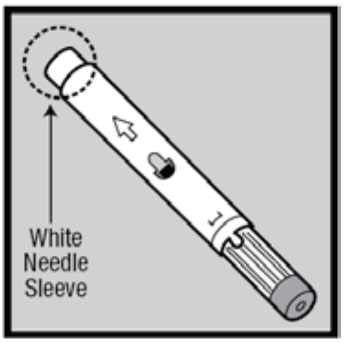
- Please note that the Pen is activated after removing Cap 2 and that pressing the button under Cap 2 will immediately result in discharge of medication.
- Do not press the plum-coloured activation button until properly positioned.
- **DO NOT RECAP as this could cause the unit to discharge**.
- Hold the Pen so that the window is in view. The presence of one or more bubbles in the window is normal.
- With your free hand, gently squeeze a sizable area of the cleaned skin at the injection site and hold firmly. You will inject into this raised area of skin.

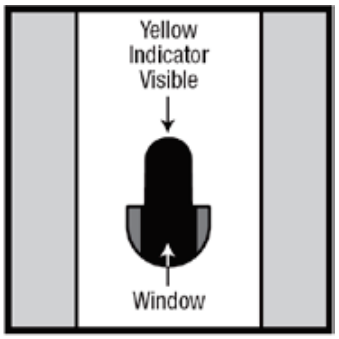
- Place the white end of the Pen straight (a 90° angle) and flat against the raised area of skin. Position the Pen so that it will not inject the needle into your fingers.
- With your index finger or thumb, press the plum-coloured button to begin the injection.
- Try not to cover the window.
- Note that you will hear a loud 'click' when you press the button, which indicates the start of the injection. You will feel a small prick as the needle advances.
- Keep pressing and continue to hold the Pen with steady pressure in place for about **10 seconds to ensure complete injection**. (A way to remember is simply 'click and count to 10'.) Do not remove the Pen while the injection is being given.
- It is important to maintain steady pressure at the injection site for the entire period of time.




- You will see a yellow indicator move into the windows during the injection. The injection is complete when the yellow indicator stops moving.

- Lift the Pen straight up from the injection site. The white needle sleeve will move down over the needle and lock into place over the needle tip. Do not try to touch the needle. The white needle sleeve is there to protect you from touching the needle.




- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do NOT rub the injection site. If you have slight bleeding, this is normal.
- Dispose of the Pen immediately into your special sharps container.

**Pre-filled Syringe**

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