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Protocol for Study M16-560

Rheumatoid Arthritis: Antibody Drug Conjugate ABBV-3373 Vs Adalimumab in Subjects with Moderate to Severe Rheumatoid Arthritis

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FULL TITLE: A Randomized, Double-Blind, Double-Dummy, Active Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABBV-3373 in Subjects with Moderate to Severe Rheumatoid Arthritis

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1 SYNOPSIS

Title: A Randomized, Double-Blind, Double-Dummy, Active Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABBV-3373 in Subjects with Moderate to Severe Rheumatoid Arthritis	
Background and Rationale:	Tumor necrosis factor (TNF)α antagonists are considered effective therapies with established safety profiles in patients with immune-mediated inflammatory diseases, including rheumatoid arthritis (RA). Nevertheless, TNFα antagonists as well as other biologics and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) provide 50% improvement in arthritis scores (ACR50) for fewer than half of RA subjects, even in combination with methotrexate (MTX), indicating that there remains an unmet clinical need for improved therapies. Glucocorticoid receptor modulators (GRMs) are potent drugs for treating many inflammatory diseases, including RA. However, the full efficacy of GRM therapy is not achieved with existing agents due to systemic side effects. ABBV-3373 is an antibody-drug conjugate (ADC) composed of adalimumab (the active component of Humira®) conjugated to A-1677770, a proprietary, highly potent GRM (also referred to as the payload) being developed for the treatment of immune-mediated inflammatory diseases including RA. This adalimumab/GRM ADC has the potential to deliver a highly potent anti-inflammatory payload selectively to the activated immune cells that express transmembrane TNF, and meanwhile to minimize systemic exposure to the free payload GRM. Therefore, the adalimumab/GRM ADC is a promising novel therapeutic agent which can achieve transformational efficacy relative to adalimumab while reducing side effects caused by free GRM systemic exposure.
Objective(s) and Endpoint(s):	Primary 1. To assess the safety, tolerability, and efficacy of ABBV-3373 administered every other week (eow) intravenously (IV) in subjects with moderately to severely active RA on background MTX. 2. To compare clinical efficacy of ABBV-3373 with adalimumab and to test the concept that an anti-TNF antibody-drug-conjugate has the potential to provide superior efficacy than the traditional anti-TNF antibody in RA. Secondary 3. To compare adalimumab with synthetic placebo control to establish assay sensitivity. 4. To assess the pharmacokinetics (PK), pharmacodynamics and immunogenicity of ABBV-3373. 5. To assess the durability of the treatment effect of ABBV-3373 after discontinuation.

	Primary Endpoint: The change in disease activity score (DAS)28 (C-reactive protein [CRP]) from Baseline (BL) at Week 12.
Investigator(s):	Multi-center.
Study Site(s):	Approximately 40 sites; United States, Puerto Rico, Germany, Hungary, Israel, Netherlands, Poland.
Study Population and Number of Subjects to be Enrolled:	The study population consists of adults with moderate to severe RA. Approximately 45 subjects will be enrolled.
Investigational Plan:	This is a randomized, double-blind, double-dummy, adalimumab active-controlled (12-week) Phase 2a study to assess the safety, tolerability, PK, pharmacodynamics, immunogenicity and efficacy following multiple IV administrations of ABBV-3373 or multiple subcutaneous (SC) injections of adalimumab in subjects with RA on background MTX. In the actively controlled period of the first 12 weeks of treatment, 45 subjects will receive either ABBV-3373 100 mg IV and the matching placebo for adalimumab SC eow or in the control arm the matching placebo for ABBV-3373 IV and adalimumab 80 mg SC eow (double-dummy) according to a 2:1 ratio. Thereafter, all subjects enter a 12-week double-blind extension period. At Week 12, the administration of ABBV-3373 will stop (i.e., the last dose of ABBV-3373 will be given at Week 10) to assess the durability of the observed clinical effects up to 24 weeks. To keep blinding of the study beyond Week 12, the subjects randomized to ABBV-3373 will receive placebo injections, whereas subjects randomized into the adalimumab arm will continue their 80 mg dosing until Week 22. At Week 12 and within the blinded extension period subjects who have not achieved at least a 20% improvement in both their swollen joint count and tender joint count based on 28 joint assessment compared with BL may be discontinued from the study at the discretion of the Investigator. Subsequently, standard of care may be administered at the discretion of the Investigator. After all endpoints are assessed at Week 24, a telephone contact is planned to follow up on safety 70 days after the last dose.
Key Eligibility Criteria:	• Subjects or their legally authorized representative must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures. • Adult male or female, between 18 and 75 years of age inclusive at Screening. • Diagnosis of RA for > 3 months based on the 1987 ACR classification criteria or 2010 ACR/European League against Rheumatism (EULAR) criteria. • Subject meets the following disease activity criteria: ≥ 4 swollen joints (based on 28 joint count) and ≥ 4 tender joints (based on 28 joint count) at Screening and BL Visits; and DAS28(CRP) ≥ 3.2 at Screening.

	• Incomplete response to MTX. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 15 mg/week) for ≥ 4 weeks prior to the first dose of study drug. Subject must be expected to be able to continue on stable dose of MTX for the duration of study participation.
Study Drug and Duration of Treatment:	ABBV-3373 (50 mg/mL) and matching placebo, adalimumab (80 mg/0.8 mL) and matching placebo. In the first 12 weeks of treatment, subjects will receive either ABBV-3373 100 mg IV and the matching placebo for adalimumab SC eow or in the control arm the matching placebo for ABBV-3373 IV and adalimumab 80 mg SC eow. At Week 12, the administration of ABBV-3373 will stop (i.e., the last dose of ABBV-3373 will be given at Week 10) to assess the durability of the observed clinical effects up to 24 weeks.
Date of Protocol Synopsis:	04 September 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Tumor necrosis factor (TNF)α antagonists reduce the signs and symptoms of disease by reducing inflammation and limiting the progression of tissue destruction and are considered effective therapies with established safety profiles in patients with immune-mediated inflammatory diseases, including rheumatoid arthritis (RA). Nevertheless, TNFα antagonists as well as other biologics and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) provide 50% improvement in arthritis scores (American College of Rheumatology 50% improvement criteria [ACR50]) for fewer than half of RA subjects, even in combination with methotrexate (MTX), indicating that there remains an unmet clinical need for improved therapies.

Glucocorticoid receptor modulators (GRMs) are potent drugs for treating many inflammatory diseases. In RA, GRMs such as prednisone are highly effective at reducing inflammation and fatigue as well as relieving pain. However, the administration of GRMs is limited due to their side effect profile including (but not limited to) hypothalamic-pituitary-adrenal (HPA) axis suppression, increased rates of bone fracture due to osteoporosis, hyperglycemia, glaucoma, skin thinning and weight gain.[1] Thus, the full efficacy of GRM therapy is not achieved with existing agents due to systemic side effects.

ABBV-3373 is an antibody-drug conjugate (ADC) composed of adalimumab (the active component of Humira®) conjugated to A-1677770, a proprietary, highly potent GRM (also referred to as the payload) being developed for the treatment of immune-mediated inflammatory diseases including RA. This adalimumab/GRM ADC has the potential to deliver a highly potent anti-inflammatory payload selectively to the activated immune cells that express transmembrane TNF, and meanwhile to minimize systemic exposure to the free payload GRM. Therefore, the adalimumab/GRM ADC is promising as a novel therapeutic agent which can achieve transformational efficacy relative to adalimumab while reducing side effects caused by free GRM systemic exposure.

Clinical Hypothesis

ABBV-3373 is safe and well-tolerated and provides superior efficacy in subjects with moderately to severely active RA on background MTX compared to adalimumab.

2.2 Benefits and Risks to Subjects

The clinical efficacy of TNF inhibitors and GRMs in the treatment of RA is well established. Based on the preclinical data discussed in the ABBV-3373 Investigator's Brochure,[2] ABBV-3373 is expected to demonstrate therapeutic benefit in treatment of RA and other immune-mediated inflammatory diseases with a favorable safety profile. Preclinical toxicology of ABBV-3373 suggests that the potential risks to human subjects receiving ABBV-3373 treatment are consistent with known effects of adalimumab and glucocorticoids (GCs). ABBV-3373 was tested in a Phase 1 single ascending dose (SAD) study in healthy volunteers in which 6 cohorts of subcutaneous (SC) (30, 100, 300 mg) and intravenous (IV) (30, 300, 900 mg) successfully completed dosing.

Medical review of the available safety data from the Phase 1 study did not identify any unexpected risk or trend to the healthy volunteer population. All single doses tested to date have been well tolerated. For further details, please see the-ABBV-3373 Investigator's Brochure.[2]

In clinical settings, TNF antagonists and GCs have been associated with an increased risk of serious infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens. Opportunistic infections have included tuberculosis (TB) and histoplasmosis. Patients will be closely monitored during the clinical study for any signs of infection.

Tumor necrosis factor antagonists have also been associated with an increased risk for malignancy (including lymphoma), hepatitis B virus (HBV) reactivation, worsening or new onset heart failure, and rarely central nervous system demyelinating disease, pancytopenia including aplastic anemia, and lupus-like syndrome.

The risk of hypersensitivity reaction or other post-dose systemic reaction for humans who receive multiple doses of ABBV-3373 is considered a potential risk. During Study M16-560, 1 case of anaphylactic shock was observed following repeated eow IV (over 3 minute bolus injection) administration of ABBV-3373. The event was assessed by the investigator and AbbVie to be reasonably related to study drug. The administration of biologics may lead to such reactions; therefore, patients will be closely monitored during and post drug administrations.

Hypertension is one of the most commonly reported events for GCs in patients, especially with high doses of GCs. Therefore, blood pressure and other vital signs will be monitored during the trial.

Based on the above considerations, the risk to RA patients receiving multiple doses of ABBV-3373 is considered manageable and acceptable. In addition, based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for RA, no change to the benefit/risk balance for subjects in this study is expected.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

1. To assess the safety, tolerability, and efficacy of ABBV-3373 administered every other week (eow) intravenously (IV) in subjects with moderately to severely active RA on background MTX.
2. To compare clinical efficacy of ABBV-3373 with adalimumab and to test the concept that an anti-TNF antibody-drug-conjugate has the potential to provide superior efficacy than the traditional anti-TNF antibody in RA.

Secondary

3. To compare adalimumab with synthetic placebo control to establish assay sensitivity.
4. To assess the pharmacokinetics (PK), pharmacodynamics, and immunogenicity of ABBV-3373.
5. To assess the duration of the treatment effect of ABBV-3373 after discontinuation.

3.2 Primary Endpoint

The primary endpoint is the change in disease activity score (DAS)28 (C-reactive protein [CRP]) from Baseline (BL) at Week 12.

3.3 Secondary and Additional Endpoints

Secondary Endpoints

1. Change in clinical disease activity index (CDAI) from BL at Week 12
2. Change in simplified disease activity index (SDAI) from BL at Week 12
3. Change in disease activity score (28 joints) (DAS28) erythrocyte sedimentation rate (ESR) from BL at Week 12
4. Achievement of low disease activity (LDA) (DAS28 [CRP] ≤3.2) at Week 12
5. Achievement of American College of Rheumatology (ACR) 50 at Week 12

Additional Endpoints

1. Change from BL in DAS28 (CRP) and DAS28 (ESR) at all visits
2. Change from BL in CDAI at all visits
3. Change from BL in SDAI at all visits
4. ACR20/50/70 response rates at all visits
5. Change from BL in individual components of ACR response at all visits
6. Achievement of LDA at all visits. Low disease activity is defined as DAS28 (CRP) ≤ 3.2, DAS28(ESR) ≤ 3.2, CDAI ≤ 10, SDAI ≤ 11
7. Achievement of clinical remission at all visits. Clinical remission is defined as DAS28 (CRP) < 2.6, DAS28(ESR) < 2.6, CDAI ≤ 2.8, SDAI ≤ 3.3
8. Change in Short Form-36 (SF-36) from BL at Week 12
9. Achievement of minimal clinically important difference (MCID) in change from BL in Health Assessment Questionnaire Disability Index (HAQ-DI) (defined as change from BL in Health Assessment Questionnaire ≤ –0.22) at all visits among subjects who have HAQ ≥ 0.22 at BL
10. Achievement of response (such as LDA) based on DAS28 (CRP), CDAI, or SDAI over time from Week 12 to Week 24 among subjects who have achieved DAS28 (CRP), CDAI, or SDAI response at Week 12

Additional endpoint definitions are provided in Appendix D.

3.4 Safety Endpoints

The following safety evaluations will be performed during the study:

1. Treatment-emergent adverse events, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, AEs of special interest
2. Percent of subjects meeting potentially clinically significant criteria for vital signs, laboratory variables, physical examination findings and electrocardiogram (ECG) interval variables

3.5 Pharmacokinetic and Immunogenicity Endpoints

Serum or plasma concentrations of the conjugated ADC (ABBV-3373), total antibody, free payload A-1677770, and adalimumab (in the comparator arm) will be determined during the treatment period and drug washout period. If sufficient data are available from the optional intensive PK sampling group, terminal elimination half-life may be calculated and reported.

Anti-drug antibody (ADA) to either ABBV-3373 or adalimumab will be evaluated and if confirmed positive, titers will be measured. If required, samples will be analyzed for neutralizing antibodies (nAb).

3.6 Biomarker Endpoints

Biospecimens (e.g., blood, serum, and plasma) will be collected at specified time points (Appendix J) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers.

The analyses of biomarker samples will include but are not limited to proteins and genetic markers that will help to understand the subject's disease and response to study treatments. Changes in cortisol level under ABBV-3373 treatment and adalimumab will be assessed. Genes of interest will include those associated with PK, genes within the target pathway, or other genes believed to be related to RA and other inflammatory diseases. Samples for ribonucleic acid (RNA) and proteomics will be used to research if any genetic variants result in changes to gene expression or protein concentrations. Biomarker samples will be collected and analyzed from all subjects, unless precluded by local regulations or restrictions. For any samples collected in Germany, the research will be restricted to study drug and RA.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, double-dummy, adalimumab active-controlled (12-week) Phase 2a study to assess the safety, tolerability, PK, pharmacodynamics, immunogenicity and efficacy following multiple IV administrations of ABBV-3373 or multiple SC injections of adalimumab in subjects with RA on background MTX. In the actively controlled period of the first 12 weeks of treatment, 45 subjects will receive either ABBV-3373 100 mg IV and the matching placebo for adalimumab SC eow or in the control arm the matching placebo for ABBV-3373 IV and adalimumab 80 mg SC eow (double-dummy) according to a 2:1 ratio. Thereafter all subjects enter a 12-week double-blind extension period. At Week 12, the administration of ABBV-3373 will stop (i.e., the last dose of ABBV-3373 will be given at Week 10) to assess the durability of the observed clinical effects up to 24 weeks. To keep blinding of the study beyond Week 12, the subjects randomized to ABBV-3373 will receive placebo injections, whereas

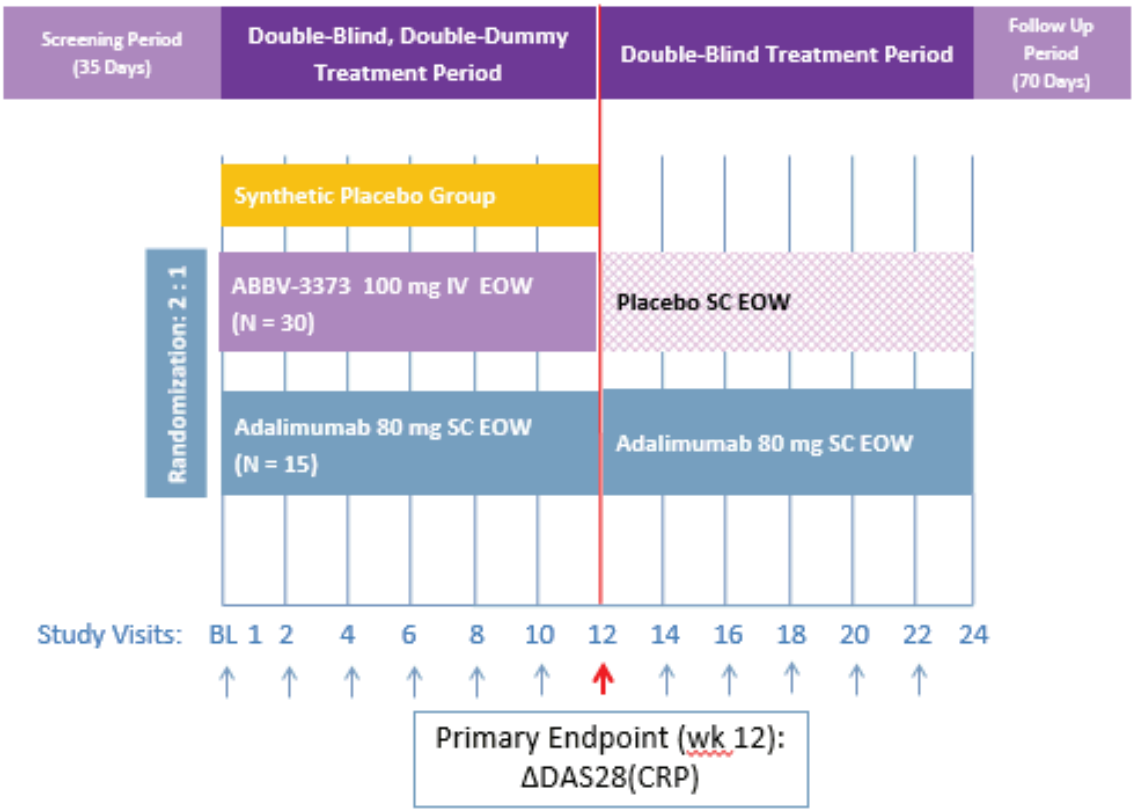
subjects randomized into the adalimumab arm will continue their 80 mg dosing until Week 22. At Week 12 and within the blinded extension period subjects who have not achieved at least a 20% improvement in both their swollen joint count (SJC) and tender joint count (TJC) based on 28 joint assessment compared with BL may be discontinued from the study at the discretion of the Investigator. Subsequently, standard of care may be administered at the discretion of the investigator.

After all endpoints are assessed at Week 24, a telephone contact is planned to follow up on safety 70 days after the last dose.

After all ongoing subjects complete the Week 12 study visit, the primary analysis for the ABBV-3373 cohort will be conducted to assess the primary/secondary endpoints and safety of this actively controlled period. A final analysis will be conducted after all subjects have completed Week 24 plus their safety follow-up. To maintain integrity of the trial, the study sites and subjects will remain blinded until the final analysis is completed.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in Appendix K.

Figure 1. Study Schematic



ΔDAS28(CRP) = change in disease activity score (DAS)28(C-reactive protein [CRP]); EOW = every other week; IV = intravenous; SC = subcutaneous

See Section 5.1 for information regarding eligibility criteria. See Section 5.8 for stratification factors for each cohort.

Pharmacokinetic Sampling

For ABBV-3373, blood samples for PK assessments will be collected according to the assessment schedule in Appendix J. Data from the first 12 subjects treated for at least 4 doses will be used in the PK interim analyses.

In addition, optional PK samples will be collected from subjects who consent to participate in the more intensive sampling group to provide data for PK characterization following repeated administrations. For these subjects, in addition to the standard sampling schedule, blood samples at the following time points will also be collected: Day 72, Day 73, Week 11, and Week 14.

4.2 Discussion of Study Design

Choice of Control Group

ABBV-3373 is an ADC, composed of adalimumab (the active component of Humira®) conjugated to A-1677770, a proprietary, highly potent GRM. In order to assess how the conjugation of adalimumab with the GRM impacts safety, tolerability and in particular whether it will provide additional efficacy versus (vs.) adalimumab, a direct comparison between the ADC and adalimumab is needed. The chosen study design with adalimumab as the positive control group allows such direct comparison. In addition, to compare clinical efficacy of the ADC with placebo control, and to address assay sensitivity, a synthetic placebo arm will be created with the propensity score matching approach using historical placebo subjects from similar trials with subject-level data.

Appropriateness of Measurements

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

Suitability of Subject Population

The specific population chosen was based on the unmet medical need of subjects as defined in Section 5.1.

Selection of Doses in the Study

Based on the clinical hypothesis, the ADC ABBV-3373 targets the activated immune cells that express transmembrane TNF to deliver the highly potent GRM selectively, therefore it has the potential to provide superior efficacy compared to a traditional anti-TNF antibody such as adalimumab. The dose of 100 mg IV eow for ABBV-3373 is selected to provide a similar systemic exposure to 80 mg adalimumab SC eow, which is a dose previously tested in RA subjects and twice as high as the recommended clinical regimen of 40 mg adalimumab SC eow. The rationale for selecting this higher dose is to increase tissue penetration of ABBV-3373 to successfully engage its intended target of transmembrane TNF on activated immune cells. Furthermore, the doses selected for ABBV-3373 and adalimumab are expected to generate similar systemic exposure to ensure a fair comparison between the two. Finally, 100 mg IV

ABBV-3373 is well within the range of doses that have been safely tested and well tolerated in the first-in-human SAD study. Historical data with adalimumab 80 mg eow or even higher in Phase 1 and 2 studies with adalimumab in the presence of MTX[3,4] or 40 mg weekly as monotherapy in Phase 2 and 3 studies[5,6] have not shown any safety concerns.

Study Duration

For the patient population selected and the type of study drug tested, a 12-week primary endpoint to analyze the improvement of signs and symptoms and to assess the safety and tolerability of ABBV-3373 is appropriate. Preclinical data from a mouse collagen induced arthritis model[2] have shown a long lasting effect of the ADC in comparison to adequate control groups. Therefore, to assess the durability of the achieved clinical response at Week 12 in ABBV-3373-treated RA subjects, the subjects will be followed closely up to Week 24. While the maintenance of responses of ABBV-3373 will be monitored (under continuous placebo injections), subjects in the comparator arm will continue their adalimumab dosing to keep the blinding of the study.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, between 18 and 75 years of age inclusive at Screening.
- 3. Body mass index (BMI) is ≥ 18.0 to ≤ 39.9 kg/m^2 after rounding to the nearest tenth. Body mass index is calculated as weight in kg divided by the square of height measured in meters.
- 4. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum values of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 2.5 × upper limit of normal (ULN);
  - Absolute neutrophil count (ANC) > 1,500/µL;
  - Creatinine < 1.5 × ULN.

- 5. Subject must have a negative test result for hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg), HBc Ab (subjects who have been vaccinated against hepatitis B [HB] and are HBs Ab positive may be enrolled), hepatitis C virus (HCV) antibody (if Hepatitis C RNA level is undetectable at Screening, the subject can participate in this trial), and human immunodeficiency virus (HIV) Ab at Screening.
- 6. Subject is willing and able to comply with procedures required in this protocol.

Diagnosis and Disease Activity

- 7. Subject has the clinical diagnosis of RA for > 3 months based on the 1987 ACR classification criteria or 2010 ACR/European League against Rheumatism (EULAR) criteria.
- 8. Subject meets the following disease activity criteria: ≥ 4 swollen joints (based on 28 joint count) and ≥ 4 tender joints (based on 28 joint count) at Screening and BL Visits; and DAS28(CRP) ≥ 3.2 at Screening.
- 9. Incomplete response to MTX. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 15 mg/week) for ≥ 4 weeks prior to the first dose of study drug. Subject must be expected to be able to continue on stable dose of MTX for the duration of study participation.

Subject History

- 10. Subject must not have been previously exposed to adalimumab or other anti-TNF biologics.
- 11. Subject must not have been previously exposed to non-anti-TNF biologics or targeted synthetic DMARDs for RA, with exception of subjects exposed for less than 3 months and terminated not due to lack of efficacy or intolerability.
- 12. No history of persistent chronic or active infection(s) requiring hospitalization or treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug administration.
- 13. No history of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
- 14. No history of moderate to severe congestive heart failure (CHF) (New York Heart Association Class III or IV).
- 15. No history or evidence of active TB disease or evidence of risk factors for latent TB infection OR a history of positive TB skin test or QuantiFERON-TB Gold In-Tube (GIT assay) within 90 days prior to study drug administration.
- 16. No history of pre-existing hyperglycemia (HbA1c > 6.5%), no history of osteoporotic fractures, and no high fracture risk (severe osteoporosis).
- 17. No history of pre-existing glaucoma, severe acne, osteonecrosis, uncontrolled hypertension, or peripheral edema.

- 18. No history of **any malignancy** except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
- 19. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 20. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 21. No history of an **allergic reaction** or significant sensitivity to any constituents of the study drug, or an anaphylactic reaction to any agent (e.g., food products and bee sting), or a major reaction to any immunoglobulin G-containing product.
- 22. Is not currently enrolled in another clinical study, and has not been previously enrolled in this study.

Contraception

- 23. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at BL prior to the first dose of study drug.
- 24. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 70 days after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
- 25. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for approximately 70 days after the last dose of study drug.

Concomitant Medications

- 26. Subject must have discontinued all conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), except for MTX. The washout periods for csDMARDs prior to the first dose of study are specified in Section 5.4.
- 27. Subject must not be on systemic GCs except for stable doses of GC (≤ 7.5 mg/d prednisone equivalent) in preceding 3 weeks prior to BL.
- 28. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug.
- 29. Subject must not have been treated with any intra-articular, intramuscular, IV, trigger point or tender point, intra-bursa, or intra-tendon sheet corticosteroids in the preceding 8 weeks prior to the first dose of the study drug.
- 30. Subject must not have received **any live vaccine** within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 12 weeks after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential

  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 70 days after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study BL Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study BL Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

Male subjects who are sexually active with a female partner of childbearing potential, must agree to use condoms, even if the male subject has undergone a successful vasectomy, from Study Day 1 through at least 70 days after the last dose of study drug.

Contraception recommendations related to use of concomitant therapies prescribed (e.g., MTX) should be based on the local label.

5.3 Prohibited Medications and Therapy

The following medications are prohibited throughout the duration of the study:

- Systemic GCs except stable doses of GC (≤ 7.5 mg/d prednisone equivalent) at BL, which have to be tapered off completely by end of Week 4.
- All csDMARDs, except MTX
- All targeted synthetic DMARDs: Examples include but are not limited to the following: Xeljanz® (tofacitinib), Olumiant® (baricitinib), Rinvoq® (upadacitinib)
- All biologic therapies. Examples include but are not limited to the following: Humira® (adalimumab), Enbrel® (etanercept), Remicade® (infliximab), Kineret® (anakinra), Rituxan® (rituximab), Cimzia® (certolizumab pegol), Simponi® (golimumab), Actemra® (tocilizumab), Raptiva® (efalizumab), Tysabri® (natalizumab), Stelara® (ustekinumab), Benlysta® (belimumab), Orencia® (abatacept), Prolia® (denosumab)
- Any intra-articular, intramuscular, parenteral, trigger point or tender point, intra-bursa, or intra-tendon sheet corticosteroids
- Any investigational drugs
- Any live vaccination

5.4 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 enrollment or receives during the study must be recorded along with reasons for use; dates of administration, including start and end dates; and dosage information including dose, route, and frequency on the appropriate electronic case report form (eCRF) through the post-treatment contact (70 day follow-up call).

Non-Steroidal Anti-Inflammatory Drugs (NSAID) and low potency analgesics (i.e., tramadol, codeine, hydrocodeine, or propoxyphene) should continue to be used for the same reason and same dose each time but should not be taken within 24 hours prior to any study visit to avoid bias in outcome measurements.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with ABBV-3373 can be located in the ABBV-3373 Investigator's Brochure.[2]

Subjects must be able to safely discontinue any prohibited medications prior to initial study drug administration as specified in Section 5.1. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Except for MTX, subject must have discontinued all csDMARDs. The washout period for csDMARDs prior to the first dose of study is specified below or should be at least five times the mean terminal elimination half-life of a drug.

- ≥ 4 weeks prior to first dose of study drug for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate or
- ≥ 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or washout with activated charcoal or as per local label).

If subjects have been exposed for less than 3 months with a non-anti-TNF biologic or targeted synthetic DMARD for RA and terminated not due lack of efficacy or intolerability, then it must be washed out for at least 5 half-lives.

Glucocorticoid Tapering of Subjects with ≤ 7.5 mg Prednisone Equivalent at BL

Up to 7.5 mg prednisone equivalent at BL is allowed. It is mandatory that subjects enrolling on concomitant GCs taper to discontinuation no later than completion of the Week 4 visit. Subjects may discontinue GCs prior to Week 4. If GC discontinuation during the first 4 weeks cannot be completed, the subject will be discontinued from the study; such subjects will be replaced.

The tapering scheme below can be considered a guide; adjustment may be required based on local availability of GC dose strengths (e.g., 5, 2.5, 2, 1 mg prednisone equivalents) and individual needs. If subjects enter with 6.5, 5.5, 4.5, 3.5, 2.5, or 1.5 mg/d then the tapering scheme for the next higher dose should be considered.

Baseline (BL)	7.5 or 7 mg/d	6 mg/d	5 mg/d	4 mg/d	3 mg/d	2 mg/d
BL to D7	5	4	2.5	2	2	1
D8 to D14	5	4	2.5	2	2	1
D15 to D21	2	2	1	1	1	1
D22 to D29	2	2	1	1	1	1
D30 onwards	0	0	0	0	0	0

5.5 Withdrawal of Subjects and Discontinuation of Study

Subjects can request to be discontinued from participating in the study at any time for any reason including but not limited to disease progression or lack of response to treatment. The Investigator may discontinue any subject's participation at any time for any reason including but not limited to disease

progression, lack of response to treatment, an AE, safety concerns, or failure to comply with the protocol. See Section 6.2 for toxicity management criteria.

Subjects will have study drug discontinued immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator or the AbbVie Therapeutic Area Medical Director (TA MD).
- Serious infections (e.g., sepsis) that cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk for continued participation in the trial as determined by the Investigator.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie TA MD.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- 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 or the AbbVie TA MD.
- The subject develops anaphylactic reactions or anaphylactic shock.

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study participation should complete a Premature Discontinuation (PD) visit.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects

should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 70-day follow-up phone call after the last dose of study drug will be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. 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 study drug, the subject should be treated in accordance with the Investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

Biomarker Research

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). Data generated from clinical study and/or biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

ABBV-3373 or matching placebo manufactured by AbbVie will be administered intravenously beginning on Day 1 (BL). Adalimumab or matching placebo manufactured by AbbVie will be administered subcutaneously beginning on Day 1 (BL). The administration of ABBV-3373 and matching placebo by venipuncture has to be given slowly over 15 – 30 minutes (via infusion line or infusion pump; the study drug can be diluted in 50 – 100 mL isotonic saline solution for this administration). Subjects have to be observed for at least 30 minutes thereafter.

AbbVie will provide study drug for ABBV-3373 or matching placebo and adalimumab or matching placebo. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

ABBV-3373 and matching placebo and adalimumab or matching placebo will be packaged in cartons with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

AbbVie will provide instructions for drug preparation (Table 1).

Table 1. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
ABBV-3373	Lyophilized powder for solution for infusion in vials	50 mg/mL when reconstituted with 1.2 mL of sterile water for injection; 1 mL extractable volume per vial; further dilution into saline for IV infusion	IV	AbbVie
Placebo for ABBV-3373	Lyophilized powder for solution for infusion in vials	N/A	IV	AbbVie
Adalimumab	Pre-filled syringe	80 mg/0.8 mL	SC	AbbVie
Placebo for Adalimumab	Pre-filled syringe	N/A	SC	AbbVie

IV = intravenous; N/A = not applicable; SC = subcutaneous

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Randomization will be stratified by factors listed in Section 4.1.

Forty-five subjects will be randomized to either the ABBV-3373 or adalimumab control arm according to a 2:1 ratio. Randomization will be stratified by the following factors:

- Stratification by current use of systemic GC (≤ 7.5 mg/d prednisone equivalent) for treatment of RA at BL (yes/no).
- Stratification by prior exposure to non-anti-TNF biologics or targeted synthetic DMARDs (< 3 months and terminated not due to lack of efficacy or intolerance) (yes/no).

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the ABBV-3373 vials and matching placebo vials, as well as adalimumab PFS and matching placebo PFS, will be provided for the study. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency. The procedure for breaking the blind is referenced in the IRT Training Slides provided to each study site.

AbbVie must be notified before the blind is broken unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. See Appendix K for contact information, including 24/7 AbbVie emergency contact coverage.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

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. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint 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 (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject 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.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

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.

If any of the following SAEs or AEs are reported, then the following supplemental report must be completed.

Serious Adverse Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	MACE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN**	Hepatic AE eCRF

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic Case Report Form; MACE = major adverse cardiac event; SAE = serious adverse event; ULN = upper limit of normal

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

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.

All adverse events reported from the time of study drug administration until 70 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Serious Adverse Event Reporting

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 a Food and Drug Administration-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects/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. In the event of an SAE, and additionally, any nonserious event of malignancy in subjects 30 years of age and younger, whether related to SC study drug or not, the physician will notify Clinical Pharmacovigilance within 24 hours of the physician becoming aware of the event by entering the SAE or nonserious event of malignancy in subjects 30 years of age and younger data into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in subjects 30 years of age and younger, that occur prior to the site having access to the RAVE® EDC system or if RAVE® is not operable, should be documented on the SAE non-case report form forms and emailed (preferred route) or faxed to the Clinical Pharmacovigilance within 24 hours of being made aware of the SAE.

Adverse Events of Special Interest

The following adverse events of special interest will be monitored during the study:

- Serious infections, opportunistic infections, herpes zoster, and TB;
- Malignancy (all types);
- Cardiovascular events (e.g., major adverse cardiovascular event [MACE]);
- Hematologic disorders (i.e., anemia, neutropenia, lymphopenia);
- Hepatic disorders;
- Hypersensitivity reactions, including all serious allergic reactions;
- Demyelinating disease;
- Systemic GC side effects (i.e., infections, skin atrophy, weight gain, cataract, hypertension, indigestion, hyperglycemia).

Adverse Event Severity and Relationship to Study Drug

The investigator will classify AEs according to the Rheumatology Common Toxicity Criteria v.2.0 (Appendix I).

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome 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 collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 70 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described in Table 2 and in the Operations Manual (Appendix K).

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

For subjects who discontinued study drug but continued study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central lab) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Management of Hypersensitivity and Serious Allergic Reactions

Subjects should be closely monitored and assessed for the development of signs and symptoms of hypersensitivity reactions, including anaphylaxis. Drug administration (ABBV-3373) should be done slowly over 15 – 30 minutes (via infusion line or infusion pump; the study drug can be diluted in 50 – 100 mL isotonic saline solution for this administration), and subjects should be observed for at least 30 minutes thereafter. Study drug should be discontinued and appropriate therapy be instituted if a subject develops clinically significant hypersensitivity reactions.

Hypersensitivity Testing

In the event of a suspected systemic post-dose hypersensitivity reaction, if the clinical situation allows, every effort should be made to obtain a serum sample within 2 hours but no later than 6 hours from symptom onset for additional blood tests (e.g, tryptase, ADA, nAb, total IgE, total hemolytic complement, etc.). Additional details regarding hypersensitivity testing can be found in the Operations Manual, Section 3.12 (Appendix K).

Management of Serious Infections

Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or a serious opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

Management of Malignancy

Subjects who develop malignancy other than NMSC or carcinoma in-situ of the cervix must be discontinued from the study drug. Information including histopathological results should be queried for the confirmation of the diagnosis.

Management of Demyelinating Disease

Subjects must be discontinued from study drug with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease (including multiple sclerosis), optic neuritis, and peripheral demyelinating disease (including Guillain Barré syndrome).

Management of Hypertension

Subjects should be closely monitored for the development of hypertension before and 30 minutes after treatment with study drug. Study drug should be interrupted if a subject develops serious hypertension in which case they should be monitored under standard of care.

Management of Hyperglycemia

Subjects should be closely monitored for the development of hyperglycemia during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious hyperglycemia in which case they should be monitored under standard of care.

Management of GC-Induced Adrenal Insufficiency

High dose or long term use of corticosteroids can produce reversible HPA axis suppression with the potential for GC insufficiency after withdrawal of treatment. Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, hormone therapy should be reinstituted in any situation of stress occurring during that period.

Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for selected abnormal laboratory values are described in Table 2, and may require a supplemental eCRF to be completed (Section 6.1 [Complaints and AEs]). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 2, the repeat testing must occur as soon as possible.

Table 2. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with new sample • If hemoglobin decreases ≥ 3.0 g/dL from BL, without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from BL and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its BL value.

Laboratory Parameter	Toxicity Management Guideline
Absolute neutrophil count (ANC)	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its BL value. • Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
Absolute lymphocyte counts (ALC)	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its BL value.
Total white blood cell count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its BL value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its BL value.

AST or ALT	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5.
	  • A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• Interrupt study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found and ALT or AST elevations persist.
	For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).
	• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Screening who develop the following should have HBV DNA PCR testing performed within one week:
	  • ALT > 5 × ULN OR
	  • ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR
	  • ALT or AST > 3 × ULN along with clinical signs of possible hepatitis.
	A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.

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

Ab = antibody; ALC = Absolute lymphocyte counts; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BL = baseline; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; eCRF = electronic case report form; HB = hepatitis B; HBV = hepatitis B virus; INR = international normalized ratio; PCR = polymerase chain reaction; TA MD = Therapeutic Area Medical Director; ULN = upper limit of normal

Management of ECG Abnormality

Subjects should be discontinued for an ECG change considered clinically significant OR a confirmed absolute QT interval corrected for heart rate using Fridericia's correction formula (QTcF) value > 500 msec.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP). All statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of the study drugs. The FAS will be used for all efficacy analyses. Subjects will be grouped according to treatment as randomized. The Per-Protocol Analysis Set represents a subset of the FAS and consists of all FAS subjects without any major violations. Additional analysis may be conducted on the Per-Protocol Analysis Set as deemed appropriate, in order to evaluate the impact of major protocol violations on the primary endpoint.

The Safety Analysis Set consists of all subjects who received at least 1 dose of the study drugs. For the Safety Analysis Set, subjects are grouped based on the treatment actually received, regardless of the treatment randomized.

7.3 Statistical Analyses for Efficacy

Primary Endpoint Analysis

Analysis of the primary endpoint will be conducted on the FAS based on treatment as randomized.

The primary endpoint is the change from BL in DAS28(CRP) at Week 12. The historical mean and standard deviation of the change from BL in DAS28(CRP) at Week 12 in adalimumab 80 mg eow are estimated to be –2.13 and 1.35 respectively based on a meta-analysis of 3 historical adalimumab studies (Studies DE007, DE009, and DE011).

The first comparison in order to achieve the first primary objective of assessing the efficacy of ABBV-3373 is to compare change from BL in DAS28(CRP) at Week 12 in the ABBV-3373 group with –2.13, the adalimumab 80 mg eow historical mean change from BL at Week 12 based on the meta-analysis. The treatment mean change from BL and 90% confidence interval of ABBV-3373 will be estimated from Mixed Effect Model Repeated Measurements (MMRM) method including up to Week 12 data with treatment group, visits, treatment-by-visit interaction, BL values of the primary endpoint, and stratification factors with observed case (OC) data. The study will be declared positive if the comparison is significant and favoring ABBV-3373.

In order to achieve the second primary objective of comparing clinical efficacy of ABBV-3373 with adalimumab and to test the concept that an anti-TNF ADC has the potential to provide superior efficacy than the traditional anti-TNF antibody in RA, the second comparison is to compare ABBV-3373 with adalimumab for the primary efficacy endpoint with a Bayesian historical data borrowing approach. The same MMRM model as described in the first comparison will be used to estimate in-study mean and standard deviation. Informative normal prior for adalimumab will be determined based on historical adalimumab data and a non-informative prior will be used for ABBV-3373. The prior distributions and estimates from MMRM model will be combined to construct the posterior distributions which will be used for comparison between ABBV-3373 and adalimumab.

If the adalimumab group mean is not comparable with historical adalimumab data, for example, the confidence intervals of the mean based on historical and in-trial data don't overlap, the Bayesian approach based on historical data will not be performed, and the mean difference in change from BL in DAS28(CRP) at Week 12 between the ABBV-3373 group and adalimumab will be estimated only based on in-study data with the MMRM model described above.

Historical data borrowing will only apply to the primary endpoint.

To address the secondary objectives of assay sensitivity, a synthetic placebo arm will be created with the propensity score matching approach using historical placebo subjects from similar trials with subject-level data. Details will be provided in the SAP.

Secondary Endpoints and Additional Endpoints Analyses for BL to Week 12

For the first 12 weeks of treatment period, continuous efficacy variables will be analyzed using an MMRM method. Categorical efficacy variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for stratification variables. Non-responder imputation (NRI) will be used for primary inference purpose. Observed Case data will be summarized descriptively as a sensitivity analysis.

Additional Endpoints Analyses up to Week 24

Statistical inference of additional continuous endpoints at each visit up to Week 24 will be conducted using analysis of covariance (ANCOVA) with treatment and stratification factors as the fixed factors and the corresponding BL value as the covariate. Additional categorical efficacy variables up to Week 24 will be analyzed using the same CMH test as for the binary secondary endpoint analysis.

Details on the analyses of the primary and other efficacy endpoints will be provided in the SAP.

Sample Size Estimation

The primary endpoint is the mean change of DAS28(CRP) from BL at Week 12. Two comparisons are considered. The first one is to compare mean change in DAS28(CRP) of the ABBV-3373 group to that of historical adalimumab 80 mg eow, which is –2.13. Assuming a mean DAS28(CRP) change from BL of –2.769 to –2.982 for ABBV-3373 (corresponding to 30% to 40% more reduction than historical adalimumab) and a standard deviation of 1.35, 30 subjects on ABBV-3373 will provide an approximate 81% to 96% power with a one-sample t-test and one-sided alpha = 0.05 significance level.

The second comparison is between ABBV-3373 arm and adalimumab arm with borrowed historical adalimumab data using a Bayesian approach. When considering borrowing historical data, the planned sample size is 45 subjects (30 in ABBV-3373 and 15 in adalimumab). The study will be considered successful if the posterior probability of mean difference < 0 is larger than 95%, i.e.,:

$$P(\mu_{ABBV-3373} - \mu_{Adalimumab} < 0 | data) > 0.95.$$

Based on the historical mean and standard deviation from adalimumab meta-analysis, a prior distribution for adalimumab is N (–2.13, 0.246^2) corresponding to the 30 historical subjects borrowed. A noninformative prior for ABBV-3373 treatment group will be set. Given the mean change from BL in DAS28 (CRP) is –2.13 for adalimumab, the probability to claim the study success is approximately 66% to 88% if the mean change from BL in DAS28 (CRP) is –2.769 to –2.982 for ABBV-3373 (i.e., 30% to 40% more reduction than historical adalimumab), with at least 45 subjects for adalimumab (15 in-trial and at least 30 borrowed) and 30 subjects for ABBV-3373. If both ABBV-3373 and adalimumab groups have the same mean change from BL of –2.13, the probability to claim study success (equivalent to type I error rate) is approximately 0.03 with the same sample sizes. In the event that adalimumab variability precludes historic data borrowing, using only the in-study 15 adalimumab subjects and 30 ABBV-3373 subjects will provide 43% to 63% power when ABBV-3373 in 30% to 40% more reduction than adalimumab respectively.

7.4 Statistical Analyses for Safety

Safety analyses will be carried out using the Safety Analysis Set. There will be 2 sets of planned safety analyses: safety analysis by Week 12 and long-term safety analysis. Safety will be assessed by AEs, laboratory assessments, and vital signs. Frequency tables of subjects with treatment emergent AEs by preferred term (PT), by system organ class (SOC) and PT as in the Medical Dictionary for Regulatory Activities, by severity, and by relationship to the study drug as assessed by the Investigator will be provided.

Summaries of SAEs, deaths, AEs leading to discontinuation, and Areas of Safety Interest will be provided as well. The changes from BL in clinical laboratory and vital sign values by visit will be analyzed in a descriptive manner. Shift of selected laboratory values from BL to defined time points will be tabulated. The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory/vital sign/ physical examination/ECG values will be summarized.

No external data borrowing will be applied for safety analyses.

7.5 Statistical Analysis of Pharmacokinetic and Immunogeniticy Data

Concentrations of conjugated ADC (ABBV-3373), total antibody, free payload A-1677770, and adalimumab (in the comparator arm), along with all applicable PK parameters will be summarized at each time point for each group using descriptive statistics.

Population PK analyses combining the data from this study and other studies may be performed and reported outside of the clinical study report.

Anti-drug antibody and nAb incidence and ADA titer values will be summarized for each group using descriptive statistics.

7.6 Statistical Analysis of Biomarker Data

Analysis will be conducted on biomarker data for the purpose of identification of prognostic, predictive, surrogate, and pharmacodynamic biomarkers associated with efficacy or safety. The association of biomarkers to the efficacy or safety endpoints will be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling approaches.

7.7 Interim Analysis

An interim PK analysis after 12 subjects are treated for at least 4 doses will be performed to assess whether the observed total antibody systemic exposure following ABBV-3373 administration is in the approximate range of 80 mg adalimumab exposure based on trough concentration (C_{trough}) levels and if there is a need for dose adjustment for ABBV-3373 and replacement of already-treated subjects.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (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 investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as last subject last visit (70 day follow-up call).

12 REFERENCES

1. Schäcke H, Döcke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002;96(1):23-43.
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4. Weisman M, Keystone E, Paulus H, et al. A dose escalation study designed to demonstrate the safety, tolerability and efficacy of the fully human anti-TNF antibody, D2E7, given in combination with methotrexate (MTX) in patients with active RA (abstract 1948). Arthritis Rheum. 2000;43(9):S391.
5. van de Putte LBA, Rau R, Breedveld F, et al. Efficacy and safety of the fully human anti-tumour necrosis factor α monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003;62(12):1168-77.
6. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying anti-rheumatic drug treatment has failed. Ann Rheum Dis. 2004;63(5):508-16.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement criteria
ACR50	American College of Rheumatology 50% improvement criteria
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BL	baseline
BMI	body mass index
CDAI	clinical disease activity index
CHF	congestive heart failure
CMH	Cochran-Mantel-Haenszel
CR	clinical remission
CRF	case report form
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
C_{trough}	trough concentration measured at the end of a dosing interval at steady state
DAS	disease activity score
DAS28	disease activity score (28 joints)
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eow	every other week
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism

FAS	full analysis set
FSH	follicle-stimulating hormone
GC	glucocorticoid
GCP	good clinical practice
GRMs	glucocorticoid receptor modulators
HAQ-DI	Health Assessment Questionnaire Disability Index
HAV	hepatitis A virus
HAV-IgM	hepatitis A virus immunoglobulin M
HB	hepatitis B
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
hs-CRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IL	interleukin
IMP	Investigational Medicinal Product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LDA	low disease activity
MACE	major adverse cardiac event
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Model Repeated Measurements
MTX	Methotrexate
nAb	neutralizing antibody
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NSAID	nonsteroidal anti-inflammatory drug

OC	observed case
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
PD	premature discontinuation
PK	pharmacokinetic(s)
PT	preferred term
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDAI	simplified disease activity index
SF-36	36-Item Short Form Health Survey
SJC	swollen joint count
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TJC	tender joint count
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analogue scale
vs.	versus

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-560: A Randomized, Double-Blind, Double-Dummy, Active Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABBV-3373 in Subjects with Moderate to Severe Rheumatoid Arthritis

Protocol Date: 04 September 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Clinical Program Development
		Medical Writing
		Immunology Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology

APPENDIX D. ADDITIONAL ENDPOINT/ASSESSMENT DEFINITIONS

Physician's Global Assessment of Disease Activity

Physician's Global Assessment of Disease Activity (visual analogue scale [VAS]) allows physicians to score on a 100 mm horizontal scale (0 being very low and 100 being very high) to assess the patient's current disease activity.

DAS28

The DAS is a combined index used to measure the disease activity in patients with RA. The DAS provides a score (between 0 and 10) indicating how active the disease is at the time of measurement. The calculation of the DAS28 score used either ESR or CRP.

The calculation of the DAS28 score will use ESR based on the following formula:

DAS28 (ESR) = 0.56 × √TJC28 + 0.28 × √SJC28 + 0.70 × ln(ESR) + 0.014 × PtGA

The calculation of the DAS28 score will use CRP based on the following formula:

DAS28 (CRP) = 0.56 × √TJC28 + 0.28 × √SJC28 + 0.36 × ln(CRP + 1) + 0.014 × PtGA + 0.96

PtGA represents patient's global assessment of disease activity; ESR is measured in mm/h, CRP is measured in mg/L, TJC28 and SJC28 represent total TJC and total SJC, respectively, based on the 28 joints (including the left and right side of the body).

American College of Rheumatology 20/50/70 Response (ACR20/50/70)

ACR20/50/70 is defined as

- At least 20%/50%/70% improvement in SJC compared to BL AND
- At least 20%/50%/70% improvement in TJC compared to BL AND
- At least 20%/50%/70% improvement in at least 3 out of the following 5 variables
    1. Patient's Assessment of RA Pain Intensity VAS
    2. Patient's Global Assessment of Disease VAS
    3. Physician's Global Assessment of Disease Activity VAS
    4. Patient's Assessment of Disability on HAQ-DI
    5. Serum high-sensitivity C-reactive protein (hs-CRP).

Clinical Disease Activity Index (CDAI)

The CDAI is a composite index for assessing disease activity based on the summation of the count of swollen/tender joint count of 28 joints along with patient and physician global assessment on visual analogue scale (VAS) (0 – 10 cm) for estimating disease activity. It has range from 0 to 76.

Simplified Disease Activity Index (SDAI)

The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28-joint assessment), patient and physician global assessment of disease activity (VAS 0 - 10 cm) and level of CRP (mg/dl, normal < 1 mg/dl). It has a range from 0 to 86.

APPENDIX E. JOINT EVALUATION WORKSHEET EXAMPLE

JOINT (Tick Correct Answer)	Subject Right						Subject Left					
	0 = Absent 1 = Present				9 = Replaced NA = No Assessment		0 = Absent 1 = Present				9 = Replaced NA = No Assessment	
	Pain/ Tenderness		Swelling		Joint		Pain/ Tenderness		Swelling		Joint	
1. Shoulder	0	1	0	1	9	NA	0	1	0	1	9	NA
2. Elbow	0	1	0	1	9	NA	0	1	0	1	9	NA
3. Wrist	0	1	0	1	9	NA	0	1	0	1	9	NA
4. Metacarpophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
5. Metacarpophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
6. Metacarpophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
7. Metacarpophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
8. Metacarpophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
9. Thumb Interphalangeal	0	1	0	1	9	NA	0	1	0	1	9	NA
10. Prox. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
11. Prox. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
12. Prox. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
13. Prox. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
14. Knee	0	1	0	1	9	NA	0	1	0	1	9	NA
TOTAL Joint Count												

APPENDIX F. REPORTED OUTCOMES VAS

APPENDIX G. HEALTH ASSESSMENT QUESTIONNAIRE DISABILITY INDEX

APPENDIX H. 36-ITEM SHORT FORM HEALTH SURVEY SAMPLE

APPENDIX I. RHEUMATOLOGY COMMON TOXICITY CRITERIA V.2.0

For designation of AE terms not shown in the Rheumatology Common Toxicity Criteria v.2.0 table, the approach described in the header row should be used.

Rheumatology Common Toxicity Criteria v.2.0

Based on Woodworth TG, et al. Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for Anti-Rheumatic Therapies.

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
A. Allergic/Immunologic				
A1. Allergic reaction/ hypersensitivity (includes drug fever)	Transient rash: drug fever < 38°C: transient, asymptomatic bronchospasm	Generalised urticaria responsive to meds; or drug fever > 38°C, or reversible bronchospasm	Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/pharyngeal oedema, requiring resuscitation
A2. Autoimmune reaction	Seriologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anaemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription meds required, slow	Corticosteroids or other prescription med with persistent disabling symptoms such as impaired exercise tolerance	NA
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g., oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy
A5. Vasculitis	Localised, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g., oral corticosteroids)	Generalised, parenteral corticosteroids required or/and short duration hospitalisation	Prolonged, hospitalisation, ischemic changes, amputation

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	2 – Moderate Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	3 – Severe Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	4 – Includes Life Threatening At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
B. Cardiac				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalisation required, parenteral meds
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value	CHF responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g., 1 + feet/calves), self-limited, no therapy required	Symptomatic (e.g., 2 + feet/calves), requires therapy	Symptoms limiting function (e.g., 3 + feet/calves, 2 + thighs), partial relief with treatment prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, transient increase by > 20 mmHg (diastolic) or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100 or by > 10 mmHg (diastolic), requiring and responding readily to treatment	Symptomatic increase > 150/100, > 20 mmHg, persistent, requiring multi agency therapy, difficult to control	Hypertensive crisis
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic, orthostatic decrease in blood pressure > 20 mmHg	Symptomatic, without interference with function, recurrent or persistent > 20 mmHg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischaemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrhythmia or/and CHF
B7. Pericarditis/ pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic NSAID required	Detectable on chest x-ray, dyspnoea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery

	1 – Mild No medication or OTC Asymptomatic, or transient Short duration (< 1 week) No change in life style	2 – Moderate Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	3 – Severe Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	4 – Includes Life Threatening At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
B. Cardiac (continued)				
B8. Phlebitis/thrombosis/ Embolism (excludes injection sites)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism
C. General (Constitutional)				
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7 – 38.5°C	Symptomatic, recurrent 38.6 – 39.9°C. Relieved by meds	≥ 40°C; ≤ 24 h, persistent symptoms; partial response to meds.	≥ 40°C, debilitating, > 24 h, hospitalisation; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.
C4. Insomnia	Difficulty sleeping, short term, no interfering with function	Difficulty sleeping interfering with function, use of prescription med.	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalisation; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds	Debilitating, hospitalisation; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring IV fluids/hospitalization > 24 hrs
C7. Weight gain	5% – 9.9%	10% – 19.9%	20% – 30%	NA
C8. Weight loss	5% – 9.9%	10% – 19.9%	20% – 30%	NA

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
D. Dermatologic				
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete, or irreversible even if patchy
D2. Bullous eruption	Localised, asymptomatic	Localised, symptomatic, requiring treatment	Generalised, responsive to treatment; reversible	Prolonged, generalised, or requiring hospitalisation for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1 – 2 wks) controlled with emollients	Generalised, interfering with ADL > 2 wks, persistent pruritis, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain, pruritis, < few days	Erythema, pain, oedema, may include superficial phlebitis, 1 – 2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery
D5. Petechiae (without vasculitis)	Few, transient asymptomatic	Dependent areas, persistent up to 2 wks	Generalised, responsive to treatment; reversible	Prolonged, irreversible, disabling
D6. Photosensitivity	Transient erythema	Painful erythema and oedema requiring topical treatment	Blistering or desquamation, requires systematic corticosteroids	Generalised exfoliation or hospitalisation
D7. Pruritis	Localised, asymptomatic, transient, local treatment	Intense, or generalised, relieved by systematic medication	Intense or generalised; poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/popular eruption; pruritis transient; TOC or no meds	Diffuse macular/popular eruption or erythema with pruritus; dry desquamation; treatment required	Generalised, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalisation; or parenteral corticosteroids

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
D. Dermatologic (continued)				
D9. Induration/ fibrosis/Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and not disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalized, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms
E. Ear/Nose/Throat				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, slowly reversible	Requires enteral support; residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	NA
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis)	Intermittent hoarseness, able to vocalise	Persistent hoarseness, able to vocalise	Whispered speech, slow return of ability to vocalise	Unable to vocalize for extended
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	2 – Moderate Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	3 – Severe Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	4 – Includes Life Threatening At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
F. Eye/Ophthalmologic				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA
F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight
F5. Vision changes (e.g., blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophtalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	2 – Moderate Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	3 – Severe Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	4 – Includes Life Threatening At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
G. Gastrointestinal				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2 – 3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4 – 6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g., incontinence, severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤ 2 units needed; responds to treatment	Haematemesis, transfusion 3 – 4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation
G6. Haematochezia (rectal bleeding)	Haemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion > 3 – 4 units	> 4 units, hypotension, requiring hospitalization
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent > 2 wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	2 – Moderate Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	3 – Severe Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	4 – Includes Life Threatening At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
G. Gastrointestinal (continued)				
G8. Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management
G9. Pancreatitis	Anylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatitic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required.
H. Musculoskeletal				
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalisation required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, responds to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non-narcotic); minor effects on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	2 – Moderate Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	3 – Severe Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	4 – Includes Life Threatening At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
I. Neuropsychiatric				
I1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation or danger to self
I2. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events	Cerebrovascular vascular accident with permanent disability
I3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily routine	Debilitating/disabling and permanent; toxic psychosis
I4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obundation, stupor	Coma
I5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	NA
I6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA
I7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	NA
I8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
I. Neuropsychiatric (continued)				
I9. Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paraethesias interfering with function	NA
I10. Seizure	NA	Recurrence of old seizures, controlled with adjustment of meds	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures
I11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalization
J. Pulmonary				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitation, requiring hospitalisation

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J. Pulmonary (continued)				
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O_2	Debilitating, not reversible; or requiring assisted ventilation
J6. Pulmonary function decreased (FVC or carbon monoxide diffusion capacity – DLCO)	76% – 90% of pre-treatment value	51% – 75% of pre-treatment value	26% – 50% of pre-treatment value	≤ 25% of pre-treatment value
Laboratory Data				
K. Haematology				
K1. Hgb (g/dl) decrease from pre-treatment	1.0 – 1.4	1.5 – 2.0	2.1 – 2.9, or Hgb < 8.0, > 7.0	≥ 3.0; or Hgb < 7.0
K2. Leukopenia (total WBC) × 1000	3.0 – 3.9	2.0 – 2.9	1.0 – 1.9	< 1.0
K3. Neutropenia (× 1000)	1.5 – 1.9	1.0 – 1.4	0.5 – 0.9	< 0.5
K4. Lymphopenia (× 1000)	1.5 – 1.9	1.0 –1.4	0.5 – 0.9	< 0.5
K5. Platelets (× 1000)	75 – LLN	50 – 74.9	20 – 49.9; platelet transfusion required	< 20; recurrent platelet transfusions

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
L. Chemistry				
L1. Hypercalcaemia (mg/dl)	1.1 × ULN – 11.5	11.6 – 12.5	12.6 – 13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycemia (mg/dl) Fasting	140 – 160	161 – 250	251 – 500	> 500, or associated with ketoacidosis
L3. Hyperkalaemia (mg/dl)	5.5 – 5.9	6.0 – 6.4	6.5 – 7.0 or any ECG change	> 7.0 or any arrhythmia
L5. Hypocalcaemia (mg/dl)	0.9 × LLN – 7.8	7.7 – 7.0	6.9 – 6.5; or associated with symptoms	< 6.5 or occurrence of tetany
L6. Hypoglycemia (mg/dl)	55 – 64 (no symptoms)	40 – 54 (or symptoms present)	30 – 39 (symptoms impair function)	< 30 or coma
L7. Hyponatraemia (mg/dl)	--	125 – 129	120 – 124	< 120
L8. Hypokalaemia (mg/dl)	--	3.0 – 3.4	2.5 – 2.9	< 2.5
L9. CPK (also if polymyositis-disease)	1.2 – 1.9 × ULN	2.0 – 4.0 × ULN	4.0 × ULN with weakness but without life-threatening signs or symptoms	> 4.0 × ULN with signs or symptoms of rhabdomyolysis or life-threatening
L10. Serum uric acid	1.2 – 1.6 × ULN	1.7 – 2.9 × ULN	3.0 – 5.0 × ULN or gout	NA
L11. Creatinine (mg/dL)	1.1 – 1.3 × ULN	1.3 – 1.8 × ULN	1.9 – 3.0 × ULN	> 3.0 × ULN
L12. SGOT (AST)	1.2 – 1.5 × ULN	1.6 – 3.0 × ULN	3.1 – 8.0 × ULN	> 8.0 × ULN
L13. SGPT (ALT)	1.2 – 1.5 × ULN	1.6 – 3.0 × ULN	3.0 – 8.0 × ULN	> 8.0 × ULN

	1 – Mild **No medication or OTC** Asymptomatic, or transient Short duration (< 1 week) No change in life style	**2 – Moderate** Symptomatic Duration (1 – 2 weeks) Alter lifestyle occasionally Meds relieve (may be prescription) Study drug continued	**3 – Severe** Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24 hr Temporary study drug discontinuation or/and dose reduced	**4 – Includes Life Threatening** At risk of death Substantial disability, especially if permanent Multiple meds Hospitalized > 24 hr Study drug discontinued
L. Chemistry (continued)				
L14. Alkaline phosphatase	1.1 – 2.0 × ULN	1.6 – 3.0 × ULN	3.0 – 5.0 × ULN	> 5.0 × ULN
L15. T. bilirubin	1.1 – 1.4 × ULN	1.5 – 1.9 × ULN	2.0 – 3.0 × ULN	> 3.0 × ULN
L16. LDH	1.3 – 2.4 × ULN	2.5 – 5.0 × ULN	5.1 – 10 × ULN	> 10 × ULN
M. Urinalysis				
M1. Haematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusion required
M2. Proteinuria (per 24 h)	300 – 500 mg (tr/1+)	501 – 1999 mg (2+)	2 – 5.0 g (3+) nephrotic syndrome	5.0 g (4+) anasarca
M3. WBC in urine	NA	NA	Indicating acute interstitial nephritis	Associated with acute renal failure
M4. Uric acid crystals	Present without symptoms	NA	With stones or symptoms of stones (e.g., renal colic)	Causing renal outflow obstruction and hospitalization

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

APPENDIX J. ACTIVITY SCHEDULE

The following table shows the required activities the subject encounters. The individual activities are described in detail in Appendix K, the **Operations Manual**.

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Study Activities Table

	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	D 72	D 73	Wk 11	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Premature Discontinuation	70-Day F/U contact
Activity	Day –35 to Day 1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 72	Day 73	Day 78	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169		
INTERVIEWS & QUESTIONNAIRES																				
Subject information and informed consent	✓																			
Eligibility criteria	✓	✓																		
Medical/surgical history	✓	✓																		
Alcohol and nicotine use	✓																			
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk assessment form	✓																			
Patient's Assessment of Pain	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
Patient's Assessment of Disease Activity	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
HAQ-DI		✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
SF-36		✓										✓						✓	✓	
LOCAL LABS & EXAMS																				
Body Weight	✓	✓										✓								
Height	✓																			
Vital Signs[a]	✓	✓	✓	✓	✓	✓	✓	✓				✓		✓		✓		✓	✓	
Physical Exam	✓	✓										✓						✓	✓	

	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	D 72	D 73	Wk 11	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Premature Discontinuation	70-Day F/U contact
Activity	Day –35 to Day 1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 72	Day 73	Day 78	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169		
12-lead ECG	✓											✓						✓	✓	
Chest x-ray	✓																			
ESR		✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
Physician's Global Assessment of Disease Activity	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
TJC28 and SJC28	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (for all female subjects of childbearing age)		✓			✓		✓					✓		✓		✓		✓	✓	
CENTRAL LABS																				
Serum pregnancy test (for all female subjects of childbearing age)	✓																			
hsCRP	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	
Hematology[b]	✓	✓	✓	✓	✓	✓	✓					✓		✓		✓		✓	✓	
Clinical chemistry and urinalysis	✓	✓		✓	✓		✓					✓		✓		✓		✓	✓	
TB Test (QuantiFERON TB Gold test and/or local purified protein derivative (tuberculin) skin test, if required)	✓																			
HIV, HAV, HBV, and HCV	✓																			
Blood samples for conjugated ADC ABBV-3373 (serum), total antibody (serum), free A-1677770 (plasma) assays, and adalimumab assays[c]		✓	✓	✓		✓		✓				✓		✓		✓		✓	✓	

	Screening	Baseline	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	D 72	D 73	Wk 11	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Premature Discontinuation	70-Day F/U contact
Activity	Day –35 to Day 1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 72	Day 73	Day 78	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169		
Blood samples for ADA assays (including ADA, nAb, and ADA titer assays)		✓										✓						✓	✓	
Blood sample for cortisol biomarker		✓	✓			✓						✓		✓					✓	
Optional PK assessments[d]									✓	✓	✓		✓							
Biomarker: Whole Blood (plasma for proteomic and targeted protein investigations)		✓	✓	✓		✓						✓		✓		✓		✓	✓	
Biomarker: Whole Blood (serum for proteomic and targeted protein investigations)		✓	✓	✓		✓						✓		✓		✓		✓	✓	
Biomarker: Whole Blood for Peripheral Blood Mononuclear Cells		✓	✓	✓		✓						✓		✓				✓	✓	
Biomarker: Whole Blood for RNA		✓	✓	✓		✓						✓		✓				✓	✓	
Biomarker: Whole Blood for DNA		✓																		
℞ TREATMENT																				
Randomization/drug assignment		✓																		
Administration study drug/placebo		✓		✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓			

a. Blood pressure will be measured prior to and 30 min after IV study drug administration (up to Week 10); otherwise, it will only be measured once.

b. HbA1c will be assessed at Screening, Week 12, and Week 24.

c. Pre-dose PK samples will be taken on dosing days. PK samples will also be taken at 1 hour and 3 hours after IV administration (from the contralateral arm) on Day 1 and Day 71.

d. Additional PK samples will be collected for subjects who consent to participating in the optional intensive PK sampling (D72, D73 and D78).

APPENDIX K. SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	18 October 2018
Version 1.1 (Germany Only)	07 November 2019
Version 1.1.1 (Germany Only)	20 November 2019
Version 2.0	20 November 2019
Version 3.0	20 November 2019
Version 4.0	11 March 2020
Version 4.1 (Germany Only)	12 March 2020

The purpose of this version is to remove the [redacted] cohort. Minor clerical edits have been made as needed for consistency and clarity throughout the protocol.

Summary of Protocol Changes:

- Title Page, removed [redacted] from the Title Page.

  Rationale: [redacted] is not being studied in this protocol.
- Synopsis, removed [redacted] language from the Synopsis.

  Rationale: [redacted] is not being studied in this protocol.
- Section 2.1, removed [redacted] language from this section and the clinical hypothesis.

  Rationale: [redacted] is not being studied in this protocol.
- Section 2.2, removed [redacted] language, and added language regarding COVID-19 related risks.

  Rationale: [redacted] is not being studied in this protocol. COVID-19 language added to indicate that no change to the benefit/risk balance for subjects in this study is expected.
- Section 3.1, removed the primary and secondary objectives for the [redacted] cohort.

  Rationale: To clarify that the [redacted] cohort is not being studied in this protocol.
- Section 3.5, revised PK and immunogenicity endpoints to remove [redacted]

  Rationale: [redacted] is not being studied in this protocol.
- Section 3.6, removed [redacted] with regard to assessment of changes in cortisol level.

  Rationale: [redacted] is not being studied in this protocol.
- Section 4.1, revised overall study design, including study schematic, and plan to exclude the [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.
- Section 4.2, removed details of study conduct related to [redacted]

Rationale: [redacted] is not being studied in this protocol.

- Section 5.1, removed prior and concomitant medication criteria and expectations for the [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.

- Section 5.1, removed washout times for prior biologics/tsDMARDs for the [redacted] cohort, and shortened duration of treatment with any investigational drug prior to first dose of study drug to 30 days.

  Rationale: [redacted] is not being studied in this protocol. Thirty days is the correct duration; the change to 70 days in the last amendment was made in error.

- Section 5.4, removed reference to [redacted] Investigator Brochure and [redacted] wash out times before baseline.

  Rationale: [redacted] is not being studied in this protocol.

- Section 5.7, removed details for [redacted] cohort dosing.

  Rationale: [redacted] is not being studied in this protocol.

- Section 5.8, removed information about randomization for the [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.

- Section 6.2, removed drug administration information for [redacted]

  Rationale: [redacted] is not being studied in this protocol.

- Section 7.3, removed statistical analyses for efficacy for [redacted]

  Rationale: [redacted] is not being studied in this protocol.

- Section 7.4, removed "of each cohort" regarding the Safety Analysis Set.

  Rationale: [redacted] is not being studied in this protocol.

- Section 7.5, removed [redacted] from statistical analysis of PK and immunogenicity data.

  Rationale: [redacted] is not being studied in this protocol.

- Section 7.7, removed interim analysis for [redacted]

  Rationale: [redacted] is not being studied in this protocol.

- Section 12, reference list updated.

  Rationale: References that are no longer applicable have been removed.

- Appendix J: revised to remove assessment/procedures related to [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.

Summary of Operations Manual Changes:

- Title Page, removed [redacted] from Title Page.

  Rationale: [redacted] is not being studied in this protocol.

- Section 1, added section description for clarity, and removed [redacted] from Pharmacokinetic Lab section.

  Rationale: [redacted] is not being studied in this protocol.
- Section 2.1, removed study activities for [redacted].

  Rationale: [redacted] is not being studied in this protocol.
- Section 3.5, removed sections for PK and immunogenicity sampling for [redacted].

  Rationale: [redacted] is not being studied in this protocol.
- Section 3.6, removed biomarker sampling for [redacted].

  Rationale: [redacted] is not being studied in this protocol.
- Section 3.12, removed clinical laboratory testing for the [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.
- Section 5.1, removed [redacted] for SUSAR reporting.

  Rationale: [redacted] is not being studied in this protocol.
- Section 6.1, removed section for [redacted] treatment administration.

  Rationale: [redacted] is not being studied in this protocol.
- Section 6.2, removed information on for [redacted] drug supply, storage, and disposition.

  Rationale: [redacted] is not being studied in this protocol.
- Section 6.3, removed the section for method of assigning subjects to treatment groups for the [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.
- Section 6.4, removed the section for timing of study drug in the [redacted] cohort.

  Rationale: [redacted] is not being studied in this protocol.

APPENDIX L. OPERATIONS MANUAL