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Protocol for Study M16-063

Rheumatoid Arthritis: A Phase 2 Study to Investigate the Safety and Efficacy of ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599 Combination) with a Background of Conventional Synthetic DMARDs in Subjects with Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs

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FULL TITLE: A Phase 2 Study to Investigate the Safety and Efficacy of ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599 Combination) with a Background of Conventional Synthetic DMARDs in Subjects with Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs

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1 SYNOPSIS

Title: A Phase 2 Study to Investigate the Safety and Efficacy of ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599 Combination) with a Background of Conventional Synthetic DMARDs in Subjects with Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs	
Background and Rationale:	ABBV-105 is a novel, covalent Bruton's tyrosine kinase (Btk) inhibitor being developed for the treatment of immune-mediated inflammatory diseases including rheumatoid arthritis (RA). Btk is a non-receptor tyrosine kinase expressed in multiple immune cell types associated with the pathogenesis of RA and other autoimmune diseases. Btk is required for the propagation of pro-inflammatory signals downstream of immunoreceptors that promote autoimmune disease pathogenesis. Compared to other Btk inhibitors, CC-292 (Celgene) and ibrutinib (Pharmacyclics/Janssen), ABBV-105 showed better potency, superior selectivity, and less off-target activity which is considered favorable for administration in humans. Upadacitinib (ABT-494) is a novel Janus kinase (JAK) inhibitor, which displays unique selectivity for the JAK1 receptor which is currently being developed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA; Phase 3), psoriatic arthritis (Phase 3), atopic dermatitis (Phase 3), Crohn's disease (Phase 3), ulcerative colitis (Phase 2), and axial spondyloarthritis (Phase 2). As of 20 June 2017, a total of 1232 subjects have received upadacitinib, which includes 469 healthy volunteers, 553 rheumatoid arthritis (RA) patients, and 210 Crohn's disease patients. Upadacitinib was generally well-tolerated and the types of adverse events (AEs) seen were typical of patients treated with immunosuppressant therapies. ABBV-105 and upadacitinib given alone or in combination with each other (as the ABBV-599 combination therapy) should be effective in decreasing signs and symptoms associated with active RA in patients with inadequate response or intolerance to biologic disease-modifying anti-rheumatic drugs (bDMARDs) by interfering with the JAK1/Btk pathways. Concurrent inhibition of JAK1/Btk pathways in RA may increase percent of those responding as well as depth of response, while maintaining an acceptable safety profile.
Objective and Endpoint(s):	The main objective of this dose-exploratory study is to evaluate the safety and efficacy of ABBV-105 and ABBV-599 (ABBV-105 plus upadacitinib) vs placebo on a background of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) for the treatment of signs and symptoms of RA at 12 weeks in bDMARD-inadequate response (bDMARD-IR) or bDMARD-intolerant subjects with moderately to severely active RA and to define optimal dose(s) for further development. Primary Endpoint: 1. Change from baseline in disease activity score (DAS)28 (C-reactive protein [CRP]) at Week 12.

	Secondary Endpoints: 2. Change from baseline in clinical disease activity index (CDAI) and simplified disease activity index (SDAI) at all visits; 3. Proportion of subjects achieving Clinical Remission (CR) at Week 12. CR is defined as DAS28 CRP < 2.6; 4. Proportion of subjects achieving low disease activity (LDA) at Week 12. LDA is defined as DAS28 CRP ≤ 3.2; 5. Proportion of subjects achieving LDA or CR based on CDAI criteria at all visits; 6. ACR20/50/70 response rates at all visits; a. ACR20/50/70 response rate will be determined based on 20%/50%/70% or greater improvement in Tender Joint Count (TJC) and Swollen Joint Count (SJC) and ≥ 3 of the 5 measures of Patient's Assessment of Pain (Visual Analog Scale [VAS]), Patient's Global Assessment of Disease Activity (PtGA), Physician's Global Assessment of Disease Activity (PhGA), Health Assessment Questionnaire Disability Index (HAQ-DI), or high-sensitivity C-reactive protein (hsCRP); 7. Change from baseline in individual components of ACR response at all visits; 8. Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]) at all visits; 9. Change from baseline in morning stiffness at all visits; 10. Change from baseline in HAQ-DI at all visits; 11. Proportion of subjects achieving minimal clinically important difference (MCID) in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3) at all visits; 12. Proportion of subjects achieving American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) Boolean remission at all visits.
Investigator(s):	Multicenter
Study Site(s):	Approximately 125 sites worldwide
Study Population and Number of Subjects to be Enrolled:	Approximately 240 male and female adult subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months and also fulfill the 2010 ACR/EULAR classification criteria for RA. Subjects have been treated for ≥ 3 months with ≥ one bDMARD but continue to exhibit active RA or had to discontinue bDMARD(s) due to intolerability or toxicity, irrespective of treatment duration.
Investigational Plan:	This is a 12-week, randomized, double-blind, parallel-group, Phase 2, multicenter study designed to assess the safety and efficacy of ABBV-105, upadacitinib, and ABBV-599 (ABBV-105 plus upadacitinib) in subjects with active RA who have had inadequate response to bDMARD therapy and are on stable background csDMARD treatment. An upadacitinib reference arm is included in the study design to aid with interpretation of ABBV-599 efficacy. The study duration will include a 35-day maximum screening period; a 12-week randomized,

	double blind, parallel-group treatment period with 30-day follow-up. Study visits will be conducted at Screening, Baseline, Week 2, Week 4, Week 8, and Week 12.

Key Eligibility Criteria:	• Adult male or female, at least 18 years old.
	• Diagnosis of RA for ≥ 3 months based on the 2010 ACR/EULAR classification criteria for RA.
	• Subject meets the following minimum disease activity criteria:
	  • ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and
	  • hsCRP ≥ 3 mg/L (central lab) at Screening Visit.
	• Subjects must have been treated for ≥ 3 months with ≥ 1 bDMARD therapy but continue to exhibit active RA or had to discontinue due to intolerability or toxicity, irrespective of treatment duration.
	• Subjects must have been receiving csDMARD therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug.
	  • The following csDMARDs are allowed (stable dose for ≥ 4 weeks prior to the first dose of study drug): oral or parenteral methotrexate (MTX) (7.5 to 25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day).
	  • A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
	• Subjects must have discontinued all bDMARDs prior to the first dose of study drug. The washout period for bDMARDs prior to the first dose of study drug is specified below or should be at least five times the mean terminal elimination half-life of a drug:
	  • ≥ 4 weeks for etanercept, adalimumab, infliximab, certolizumab, golimumab, tocilizumab, and abatacept;
	  • ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pretreatment level or normal reference range (central lab) if pretreatment levels are not available (TBNKM cell testing may be completed at Screening rather than Baseline if B cell testing is indicated).
	  • Subject must not have prior exposure to any JAK inhibitor for greater than 2 weeks (including but not limited to upadacitinib, tofacitinib, baricitinib, and filgotinib). A washout period of ≥ 30 days is required for any JAK inhibitor prior to the first dose of study drug.

Study Drug and Duration of Treatment:	Study drug will be taken orally as ABBV-105 and/or matching placebo capsules and upadacitinib and/or matching placebo tablet once daily with or without food. The ABBV-105 arms will be administered 3 oral capsules of ABBV-105 totaling doses of 5 mg, 20 mg, or 60 mg once daily (QD) and 1 tablet of

	upadacitinib placebo. The ABBV-599 arm will be administered oral capsules of ABBV-105 totaling a dose of 60 mg combined with 1 oral tablet of upadacitinib 15 mg QD. The upadacitinib arm will be administered 3 capsules ABBV-105 placebo and 1 oral tablet of upadacitinib 15 mg QD. Approximately 240 subjects who meet eligibility criteria will be randomized in a 3:2:2:2:2:1 ratio to 1 of 6 treatment groups: • ABBV-105 60 mg and upadacitinib 15 mg QD (n = 60) • ABBV-105 60 mg and upadacitinib placebo QD (n = 40) • ABBV-105 20 mg and upadacitinib placebo QD (n = 40) • ABBV-105 5 mg and upadacitinib placebo QD (n = 40) • ABBV-105 placebo and upadactinib 15 mg QD (n = 40) • ABBV-105 placebo and upadacitinib placebo QD (n = 20)
Date of Protocol Synopsis:	15 October 2019

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

ABBV-105 is a novel, covalent Bruton's tyrosine kinase (Btk) inhibitor being developed for the treatment of immune-mediated inflammatory diseases including rheumatoid arthritis (RA).

Btk is a non-receptor tyrosine kinase expressed in multiple immune cell types associated with the pathogenesis of RA and other autoimmune diseases. Btk is required for the propagation of pro-inflammatory signals downstream of immunoreceptors that promote autoimmune disease pathogenesis. Compared to other Btk inhibitors, CC-292 (Celgene) and ibrutinib (Pharmacyclics/Janssen), ABBV-105 showed better potency, superior selectivity, and less off-target activity which is considered favorable for administration in humans.

The hematopoietic expression and signaling function of Btk downstream of numerous receptors has raised interest in pharmacologic targeting of Btk for immune-mediated inflammatory diseases including RA.[1] The potential clinical value of Btk inhibition has been supported by studies in preclinical models of arthritis and lupus.[2,3] These have demonstrated: 1) complete abrogation of arthritis in the collagen-induced arthritis model when initiated at disease onset, consistent with the effect of Btk inhibition on autoantibody production,[2,3] 2) efficacy in myeloid-mediated animal arthritis models, consistent with the effects of Btk inhibition on macrophage, mast cell, dendritic cell, and neutrophil activity,[2,3] and 3) marked reductions of proteinuria in mouse models of lupus, consistent with the effect of Btk inhibition on autoantibody production and/or myeloid cell activation.[4-6]

Upadacitinib is a novel Janus kinase (JAK) inhibitor, which displays unique selectivity for the JAK1 receptor which is currently being developed for the treatment of adult patients with moderately to severely active RA (Phase 3), psoriatic arthritis (Phase 3), atopic dermatitis (Phase 3), Crohn's disease (Phase 3), ulcerative colitis (Phase 2), and axial spondyloarthritis (Phase 2). As of 20 June 2017, a total of 1232 subjects have received upadacitinib, which includes 469 healthy volunteers, 553 RA patients, and 210 Crohn's disease patients. Upadacitinib was generally well-tolerated, and the types of adverse events (AEs) seen were typical of patients treated with immunosuppressant therapies.

Clinical Hypothesis

ABBV-105 given alone or in combination with upadacitinib (as the ABBV-599 combination therapy) should be effective in decreasing signs and symptoms associated with active RA in patients with inadequate response or intolerance to biologic disease-modifying anti-rheumatic drugs (bDMARDs) by interfering with the JAK1/Btk pathways. Concurrent inhibition of JAK1/Btk pathways in RA may increase percent of those responding as well as depth of response (relative to inhibiting either pathway alone), while maintaining an acceptable safety profile.

2.2 Benefits and Risks to Subjects

Preclinical toxicology studies of ABBV-105 in animals and ex vivo human samples suggest that the potential risks to human subjects of ABBV-105 treatment are anemia, bleeding associated with platelet dysfunction, and lymphopenia. Reductions in lymphocytes and the known mechanism of action suggest the potential for an increased susceptibility to infection.

In Phase 1 Studies M16-356 (single doses of ABBV-105 ranging from 2 to 125 mg), M16-357 (multiple doses of ABBV-105 ranging from 3 - 60 mg), and M16-044 (co-administration of upadacitinib 30 mg with ABBV-105 ranging from 10 - 60 mg), ABBV-105 alone or ABBV-105 co-administration with upadacitinib was well-tolerated with no serious adverse events (SAEs) observed in healthy adult subjects.

Taken together, the safety data from the Phase 1 program support further development of ABBV-105 given alone or in combination with upadacitinib (ABBV-599) in Phase 2 in subjects with RA.

For safety monitoring, the following are included in the protocol:

- Exclusion of subjects with chronic or recent infections;
- Screen subjects for tuberculosis (TB); exclude patients with active TB or latent TB without history of appropriate prophylaxis: latent TB as assessed by Interferon Gamma Release Assay (IGRA) QuantiFERON Tuberculosis (TB) Gold in Tube Test or equivalent (i.e., or T SPOT.*TB* test; as available and if compliant with local TB guidelines) and/or a purified protein derivative (PPD) test (or both if required per local guidelines).
- Subjects will also be screened for human immunodeficiency virus (HIV) and hepatitis B and C.
- If a subject develops a serious infection or opportunistic infection with study treatment, study drug should be interrupted and appropriate treatment of the infection should be initiated.
- Review SAEs of infection on a real time basis and query for additional information as clinically indicated
- A supplemental herpes zoster form will be used to collect additional information for any herpes zoster infections.

See Section 3.4 for information on the Data Monitoring Committee (DMC).

For further details, please see findings from completed studies, including safety data in the ABBV-105 and upadacitinib Investigator's Brochures.[7,8]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The main objective of this dose exploratory study is to evaluate the safety and efficacy of ABBV-105 and ABBV-599 (ABBV-105 plus upadacitinib) vs placebo on a background of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) for the treatment of signs and symptoms of RA at 12 weeks

in bDMARD-inadequate response (bDMARD-IR) or bDMARD-intolerant subjects with moderately to severely active RA and to define optimal dose(s) for further development.

3.2 Primary Endpoint

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

3.3 Secondary Endpoints

2. Change from baseline in clinical disease activity index (CDAI) and simplified disease activity index (SDAI) at all visits;
3. Proportion of subjects achieving Clinical Remission (CR) at Week 12. CR is defined as DAS28 CRP < 2.6;
4. Proportion of subjects achieving low disease activity (LDA) at Week 12. LDA is defined as DAS28 CRP ≤ 3.2;
5. Proportion of subjects achieving LDA or CR based on CDAI criteria at all visits;
6. ACR20/50/70 response rates at all visits;
    a. ACR20/50/70 response rate will be determined based on 20%/50%/70% or greater improvement in Tender Joint Count (TJC) and Swollen Joint Count (SJC) and ≥ 3 of the 5 measures of Patient's Assessment of Pain (Visual Analog Scale [VAS]), Patient's Global Assessment of Disease Activity (PtGA), Physician's Global Assessment of Disease Activity (PhGA), Health Assessment Questionnaire Disability Index (HAQ-DI), or high-sensitivity C-reactive protein (hsCRP);
7. Change from baseline in individual components of American College of Rheumatology (ACR) response at all visits;
8. Change from baseline in DAS28(CRP) and DAS28 (erythrocyte sedimentation rate [ESR]) at all visits;
9. Change from baseline in morning stiffness at all visits;
10. Change from baseline in HAQ-DI at all visits;
11. Proportion of subjects achieving minimal clinically important difference (MCID) in change from baseline in HAQ-DI (defined as change from baseline in HAQ-DI ≤ –0.3) at all visits;
12. Proportion of subjects achieving ACR/European League Against Rheumatism (EULAR) Boolean remission at all visits.

3.4 Safety Assessments

Routine safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

SAEs will be assessed at any dose that results in a death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly.

Safety data will be assessed over the course of the study. An independent internal DMC will be created, and unblinded safety assessments will be conducted (Section 7.5). This is to assess unanticipated safety signals with regard to novel agents ABBV-105 and ABBV-599.

An independent Cardiovascular Adjudication Committee (CAC) will adjudicate blinded cardiac and cerebrovascular events. A CAC charter will be prepared separately from the protocol that will define objective, scope, frequency, and triggers of data reviews.

3.5 Pharmacokinetic Endpoints

ABBV-105 and upadacitinib plasma concentrations will be summarized at each sampling time point using descriptive statistics (Appendix D). A mixed-effects modeling approach may be used to estimate the population central value and the empirical Bayesian estimates of the individual values for ABBV-105 and upadacitinib oral clearance (CL/F) and volume of distribution (V_{ss}/F). Additional parameters may be estimated if useful in the interpretation of the data.

3.6 Biomarker Research

Whole blood samples will be collected at specific time points (Appendix D) throughout the study to evaluate known and or novel disease related or drug related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The analyses may include but are not limited to prognostic, surrogate, predictive and pharmacodynamic biomarkers. This research is exploratory in nature and the results may not be included with the clinical study report. Biomarker samples will be collected and analyzed from all subjects, unless precluded by local regulations or restrictions. Research on samples collected in Germany will be restricted to ABBV-105, upadacitinib, and RA.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a 12-week, randomized, double-blind, parallel-group, Phase 2, dose exploratory, multicenter study designed to assess the safety and efficacy of ABBV-105 and ABBV-599 in subjects with active RA who have had inadequate response to bDMARD therapy and are on stable background csDMARD treatment. Subjects who meet eligibility criteria will be randomized in a 3:2:2:2:2:1 ratio to 1 of 6 treatment groups:

- Group 1: Upadacitinib 15 mg and ABBV-105 60 mg administered once daily (QD) (n = 60)
- Group 2: ABBV-105 60 mg and upadacitinib placebo QD (n = 40)
- Group 3: ABBV-105 20 mg and upadacitinib placebo QD (n = 40)
- Group 4: ABBV-105 5 mg and upadacitinib placebo QD (n = 40)

- Group 5: Upadacitinib 15 mg and ABBV-105 placebo QD (n = 40)
- Group 6: ABBV-105 placebo and upadacitinib placebo QD (n = 20)

The study duration will include a 35-day maximum screening period and a 12-week randomized, double blind, parallel-group treatment period with 30-day follow-up. Study visits will be conducted at Screening, Baseline, Week 2, Week 4, Week 8, and Week 12. For post-baseline visits, a visit window of ± 3 days will be allowed.

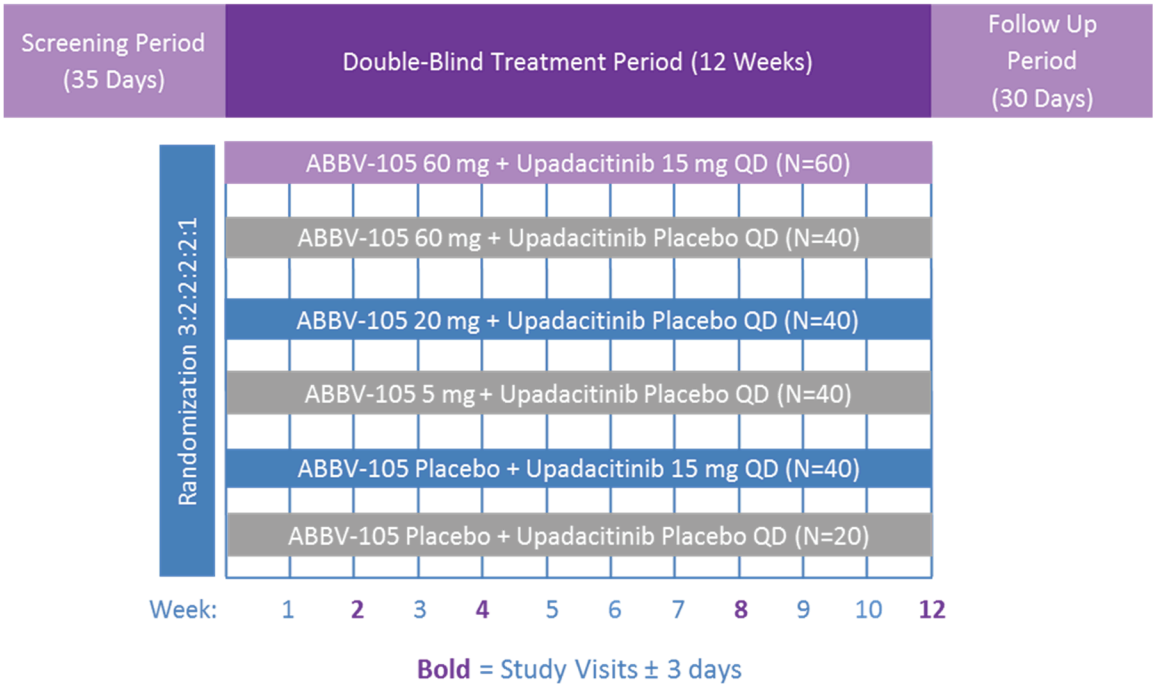
The schematic of the study is shown in Figure 1.

The study population will consist of adult subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months and also fulfill the 2010 ACR/EULAR classification criteria for RA. Subjects will have been treated for ≥ 3 months with ≥ one bDMARD but continue to exhibit active RA or had to discontinue bDMARD(s) due to intolerability or toxicity, irrespective of treatment duration.

Randomization will be stratified by number of prior bDMARDs used (failed 1 or 2 biologics with the same mechanism of action; failed ≥ 3 biologics with the same mechanism of action and/or ≥ 2 bDMARDs with different mechanisms of action). Once approximately 35% of the total subjects have been randomized to the second stratum, further screening of subjects in that group may be suspended. See Section 5.1 for information regarding eligibility criteria.

This study will be conducted in approximately 240 subjects with planned interim safety reviews as discussed in Section 7.5.

Figure 1. Study Design



QD = once daily

4.2 Discussion of Study Design

Choice of Control Group

This is a parallel-group study consisting of 6 treatment groups receiving ABBV-105, ABBV-599 (a combination of upadacitinib and ABBV-105), upadacitinib, or matching placebo to assess the safety and efficacy of ABBV-105 given alone or in combination with upadacitinib (as the ABBV-599 combination) once daily for 12 weeks in patients with active RA who have had an inadequate response or intolerance to bDMARDs. Placebo will serve as a reference for efficacy assessment while the additional efficacy of ABBV-599 combination will utilize in-study upadacitinib subjects as a reference (with/without historic data borrowed from Phase 2 and Phase 3 upadacitinib studies performed in similar populations).

Appropriateness of Measurements

Appropriate 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

Adult subjects who are at least 18 years of age with a diagnosis of RA for ≥ 3 months and also fulfill the 2010 ACR/EULAR classification criteria for RA and who have been treated for ≥ 3 months with ≥ 1 bDMARD, but continue to exhibit active RA or had to discontinue bDMARD(s) due to intolerability or toxicity, irrespective of treatment duration, are eligible for this study. The selection criteria relating to safety guarantee that subjects enrolled can be safely treated with ABBV-105, with or without upadacitinib, based on the current knowledge of these drugs.

Selection of Doses in the Study

The dose selection in this study is based on analysis of pharmacokinetic, pharmacodynamic, safety, and efficacy (upadacitinib only) data from Phase 1 studies in healthy volunteers for ABBV-105 and Phase 2 and Phase 3 studies for upadacitinib.

Given the uncertainty in correlation between blood Btk occupancy and efficacy in RA patients, the low and middle ABBV-105 doses are intended to target exposures that would approximate mid-level and near maximal Btk occupancy, respectively, in a dosing interval, and the high dose is intended to approximate exposures at or greater than those needed to achieve maximal Btk occupancy.

In the Phase 1 ABBV-105 multiple ascending dose study (Study M16-357), the Btk occupancy at steady-state was near 100% throughout the dosing interval at the 60 mg QD dose; in the ABBV-599 multiple ascending dose study (Study M16-044), the Btk occupancy of approximately 70% and 90% was maintained throughout the dosing interval at the 10 and 20 mg QD doses, respectively.

Following once-daily dosing of ABBV-105 5 mg, 20 mg, and 60 mg, peak Btk occupancy at steady-state is predicted to be 67%, 93%, and 99%, respectively, whereas steady-state trough Btk occupancy is predicted to be 58%, 83%, and 89%, respectively. Therefore, the ABBV-105 doses of 5, 20, and 60 mg were selected to satisfy the Btk-related exposure criteria, as well as to represent exposures that were found to be safe and well tolerated in the Phase 1 studies. The selected dose of the upadacitinib component of the ABBV-599 arm is 15 mg, based on the results of the upadacitinib RA Study M13-542.

In bDMARD-IR subjects with RA, upadacitinib 15 and 30 mg QD doses achieved superior responses to placebo in all primary and ranked secondary endpoints at Weeks 12 and 24. The upadacitinib 30 mg dose provided little additional incremental benefit over the 15 mg dose. Thus, for the ABBV-599 treatment arm, the 15 mg QD upadacitinib dose was selected to be co-administered with ABBV-105. A treatment arm of 15 mg QD upadacitinib with ABBV-105 placebo QD is included to provide an in-study reference to estimate the additive effect of the ABBV-599 combination relative to upadacitinib monotherapy.

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**, at least 18 years old.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum alanine transaminase (ALT) < 2 × upper limit of normal (ULN)
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula > 40 mL/min/1.73 m^2
  - Total white blood cell (WBC) count > 3,000/µL
  - Absolute neutrophil count (ANC) > 1,500/µL
  - Platelet count > 100,000/µL
  - Absolute lymphocyte count > 800/µL
  - Hemoglobin > 10 g/dL

Disease Activity

- 4. Diagnosis of RA for ≥ 3 months based on the 2010 ACR/EULAR classification criteria for RA.
- 5. Subject meets the following minimum disease activity criteria:
  - ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits (Appendix E); and

- hsCRP ≥ 3 mg/L (central lab) at Screening Visit.

Subject History

- 6. No history of any of the following cardiovascular conditions:
  - Moderate to severe congestive heart failure (New York Heart Association Class III or IV).
  - Recent history (within past 6 months) of cerebrovascular accident (CVA), myocardial infarction, and/or coronary stenting.
  - Uncontrolled hypertension as defined by a persistent systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg. For subjects with known hypertension, the subject's BP must be stable for at least 4 weeks on current, stable anti-hypertensive medications.
  - Prior unprovoked deep vein thrombosis (DVT) or pulmonary embolism (PE) (i.e., any spontaneous event not directly attributable to trauma or vascular instrumentation).
  - Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.
- 7. No history of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms], or any arthritis with onset prior to age 17 years). Current diagnosis of secondary Sjogren's Syndrome is permitted.
- 8. Must not have been treated with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the preceding 8 weeks prior to the first dose of study drug.
- 9. Must not have been treated with any investigational drug within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.
- 10. Females must not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
- 11. For all females of child-bearing potential: a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 12. 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 30 days. Female subjects of non-childbearing potential do not need to use birth control.
- 13. Must not have any active or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or HIV.

  Active HBV, HCV, and HIV are defined as:

- HBV: Hepatitis B surface antigen (HBs Ag) positive (+) or, for hepatitis B core antibody (HBc Ab) positive subjects, detection of HBV DNA by polymerase chain reaction (PCR);
- HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab);
- HIV: Confirmed positive anti-HIV antibody (HIV Ab) test.

14. Must not have active TB or meets TB exclusionary parameters (defined as the presence of active TB or latent TB not adequately treated as per protocol requirements).

    Canada only: Must not have active TB or untreated or inadequately treated latent TB

- Must not have evidence of active TB defined in this study as the following:
    i. Documented by a positive purified protein derivative (PPD) test (≥ 5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history) and/or medical history, clinical features, and abnormal chest x-ray at screening consistent with active TB.
    ii. The QuantiFERON®-TB Gold test or T SPOT.*TB* test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.
- Must not have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:
    i. Documented to have a positive PPD test (≥ 5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
    ii. PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON-TB Gold test or T SPOT.*TB* test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); or
    iii. QuantiFERON®-TB Gold test or T SPOT.*TB* test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).

15. Must not have used known strong cytochrome P450 (CYP)3A or CYP1A2 inhibitors or strong CYP3A or CYP1A2 inducers from Screening through the end of the study.

16. Must not have had receipt of 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 4 weeks after the last dose of oral study drug.

17. Must not have a history of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.

- 18. Must not have a history of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
- 19. Must not have a history of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for gastrointestinal perforation per investigator judgment.
- 20. Must not have any conditions that could interfere with drug absorption including but not limited to short bowel syndrome.
- 21. Must not be a recipient of an organ transplant.
- 22. Must not have history of clinically significant medical conditions or any other reason that in the opinion of the Investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
- 23. Must not have had an active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug.
- 24. Must not have a history of an allergic reaction or significant sensitivity to constituents of the study drugs (and its excipients) and/or other products in the same class.

Concomitant Medications

- 25. Subjects must have been treated for ≥ 3 months with ≥ 1 bDMARD therapy but continue to exhibit active RA or had to discontinue due to intolerability or toxicity, irrespective of treatment duration.
- 26. Subjects must have been receiving csDMARD therapy ≥ 3 months and on a stable dose for ≥ 4 weeks prior to the first dose of study drug.
    - The following csDMARDs are allowed (stable dose for ≥ 4 weeks prior to the first dose of study drug): oral or parenteral methotrexate (MTX) (7.5 to 25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day).
    - A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.
- 27. Dose of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen/paracetamol must have been at a stable dose ≥ 1 week prior to the first dose of study drug; oral corticosteroids (equivalent to prednisone ≤ 10 mg/day) or inhaled corticosteroids for stable medical conditions are allowed but must have been at a stable dose ≥ 4 weeks prior to the first dose of study drug.
- 28. Subjects must have discontinued all bDMARDs prior to the first dose of study drug. The washout period for bDMARDs prior to the first dose of study drug is specified below or should be at least five times the mean terminal elimination half-life of a drug:
    - ≥ 4 weeks for etanercept, adalimumab, infliximab, certolizumab, golimumab, tocilizumab, and abatacept;

- ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pretreatment level or normal reference range (central lab) if pretreatment levels are not available (B cell testing may be completed at Screening if indicated).

29. Subjects must have discontinued all high-potency opiates at least 1 week and oral traditional Chinese medicine for at least 4 weeks prior to the first dose of study drug (refer to Section 5.3 for prohibited medications).

30. Subject must not have prior exposure to any JAK inhibitor for greater than 2 weeks (including but not limited to upadacitinib, tofacitinib, baricitinib, and filgotinib). A washout period of ≥ 30 days is required for any JAK inhibitor prior to the first 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 a follicle stimulating hormone (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 30 days after the last dose of study drug. Females must commit to one of the following methods of birth control with:

  - Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
  - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study 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).
  - To have a vasectomized sexual partner(s) (the vasectomized partner[s] has received medical assessment of the surgical success and is the sole sexual partner of the trial subject).

- To practice true abstinence (if acceptable per local requirements), 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). A condom is required in the following countries: UK, Germany, and Spain.

The concomitant csDMARDs (i.e., MTX, sulfasalazine, etc.) that have been prescribed per standard of care prior to study entry and are allowed to be continued during the study for female and male subjects. Contraception should continue while the subject is on the concomitant csDMARD(s) and that duration of contraception after discontinuation of the csDMARD(s) should be based on the local label. Additional local requirements may apply.

5.3 Prohibited Medications and Therapy

JAK Inhibitor

Prior exposure to JAK inhibitors (including but not limited to upadacitinib, tofacitinib [Xeljanz®], baricitinib [Olumiant®], and filgotinib) must not be greater than 2 weeks.

Corticosteroids

Oral corticosteroids > 10 mg prednisone/day or equivalent and intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids are NOT allowed during this study.

Any csDMARD/Immunosuppressive Not Listed in Section 5.4 (Prior and Concomitant Therapy)

All biologic therapies are prohibited during the study.

Subjects must have discontinued the bDMARD prior to the first dose of study drug as specified in the washout procedures (Eligibility Criterion #28). For all other bDMARDs, contact the Therapeutic Area Medical Director for the washout period required prior to the first dose of study drug.

Examples of biologic therapies 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)

Strong CYP3A or CYP1A2 Inhibitors or Inducers

Systemic use of known strong inhibitors or inducers of CYP3A or CYP1A2 is excluded from the Screening Visit through the end of the study. The most common strong CYP3A or CYP1A2 inhibitors and inducers are listed in Table 1.

Table 1. Examples of Commonly Used Strong CYP3A or CYP1A2 Inhibitors and Inducers

Strong CYP3A Inhibitors	**Strong CYP3A Inducers**
Boceprevir Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Carbamazepine Phenytoin Rifampin Rifapentine St. John's Wort
Strong CYP1A2 Inhibitors	**Strong CYP1A2 Inducers**
Fluvoxamine Ciprofloxacin Enoxacin Zafirlukast	Rifampin

Live Vaccines

Use of live vaccines is prohibited during the study. Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Herpes zoster;
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid.

Elective and Emergency Surgeries

Elective surgery will not be allowed during the study until the primary endpoint has been assessed. If the subject undergoes emergency surgery, the study drug should be interrupted as soon as possible and reintroduced once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

5.4 Prior and Concomitant Therapy

Subjects should continue on their stable (≥ 4 weeks prior to the first dose of study drug) background csDMARD therapy, restricted to the following: oral or parenteral MTX (7.5 to 25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day). Combinations of up to two csDMARDs are allowed except for the combination of MTX and leflunomide.

At any time, the csDMARD dose may be decreased only for safety reasons. Subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent, such as folinic acid) throughout study participation. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions. AbbVie will not provide the csDMARDs (or folic acid, if taking MTX).

Subjects should continue on their stable doses of NSAIDs, acetaminophen/paracetamol, oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids.

- If taking any of the above on a scheduled basis, they should continue to take them as they did at study entry with no change in dose or frequency, including on study visit days.

- If not taking any of the above at baseline, these should not be initiated.
- If taking any of the above, including low potency analgesics (i.e., tramadol, codeine, hydrocodone, or propoxyphene) at baseline on an as needed (PRN) basis, they should continue to use them for the same reason and same dose each time, but they should not be taken within the 24 hours prior to any study visit to avoid bias in outcome measurements.

In the event of tolerability (or other safety) issues, the doses of these medications may be decreased or discontinued with substitution of another permitted medication from that class. PRN use of inhaled corticosteroids is permitted at any time.

A long-term extension (LTE) study is planned to be conducted under a separate protocol at sites where it is permitted by the local Competent Authority and Ethics Committee. Patient rollover from the initial randomized portion of the study will occur at Week 12 for all patients to assure comparable length of exposure for each different treatment.

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.

- Subject develops a gastrointestinal perforation.

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment or study participation should complete a Premature Discontinuation visit (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 30-day follow-up phone call after the last dose of study drug may 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 electronic case report form (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.

If a subject withdraws from the main study, biomarker research samples will continue to be stored and analyzed. A subject must contact the study investigator if they no longer want their samples to be stored and analyzed. Once AbbVie is notified, no new information will be collected, no new analysis will be started, and the samples will be destroyed unless a regulatory authority requires AbbVie to keep them. However, if AbbVie (or people or companies working with AbbVie) collected any information or did any testing before withdrawal, AbbVie (or people or companies working with AbbVie) will still use and disclose such information, use the test results, and keep the data generated from the samples.

5.7 Study Drug

ABBV-105, upadacitinib, or matching placebo manufactured by AbbVie will be administered on Day 1 (Baseline) and should be taken at approximately the same time each day. Subjects will be instructed to take study drug orally, which includes only 1 capsule of ABBV-105 or placebo from each of the 3 dispensed bottles per day, with or without food, and only 1 tablet of upadacitinib or placebo from the dispensed bottle per day, with or without food. Subjects will be instructed to take only 1 tablet from the dispensed tablet bottle per day. If subjects should forget to take their ABBV-105, upadacitinib, or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 10 hours before their next scheduled dose. Otherwise they should take the next dose at the next scheduled dosing time.

Subject dosing will be recorded on a subject dosing diary. The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. Study site personnel will document compliance.

AbbVie will not supply drug other than ABBV-105, upadacitinib, or matching placebo.

ABBV-105, upadacitinib, and matching placebo will be packaged in bottles 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.

Table 2. Study Drug

	Investigational Product	Investigational Product	Investigational Product Placebo	Investigational Product Placebo
Investigational product name	ABBV-105	Upadacitinib	ABBV-105 Placebo	Upadacitinib Placebo
Active ingredient	ABBV-105	Upadacitinib	N/A	N/A
Mode/Route of Administration	Oral	Oral	Oral	Oral
Combination Drugs	N/A	N/A	N/A	N/A
Formulation				
Dosage Form	Capsule	Film-Coated Tablet	Capsule	Film-Coated Tablet
Dose and Units	5 mg, 20 mg	15 mg	N/A	N/A
Drug Preparation	N/A	N/A	N/A	N/A
Masking	N/A	N/A	N/A	N/A
Frequency of Administration	Daily	Daily	Daily	Daily
Storage Conditions	Room Temperature (15° – 25°C/ 59° to 77°F)	Room Temperature (15° – 25°C/ 59° to 77°F)	Room Temperature (15° – 25°C/ 59° to 77°F)	Room Temperature (15° – 25°C/ 59° to 77°F)

5.8 Randomization/Drug Assignment

A total of 240 subjects who meet eligibility criteria will be randomized in a 3:2:2:2:2:1 ratio to 1 of 6 treatment groups:

- ABBV-105 60 mg and upadacitinib 15 mg QD (n = 60)
- ABBV-105 60 mg and upadacitinib placebo QD (n = 40)
- ABBV-105 20 mg and upadacitinib placebo QD (n = 40)
- ABBV-105 5 mg and upadacitinib placebo QD (n = 40)
- ABBV-105 placebo and upadacitinib 15 mg QD (n = 40)
- ABBV-105 placebo and upadacitinib placebo QD (n = 20)

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 number of prior bDMARD use (failed 1 or 2 biologics with the same mechanism of action; failed ≥ 3 biologics with the same mechanism of action and/or ≥ 2 biologics with

multiple mechanisms of action). Once approximately 35% of the total subjects have been randomized to the second group, further screening of those subjects may be suspended.

Once approximately 30% of total subjects have been randomized who are not on MTX, further screening of such subjects may be suspended.

Once approximately 30% of total subjects have been randomized who are active smokers, further screening of such actively smoking subjects may be suspended.

Once approximately 30% of total subjects have been randomized who are negative for both rheumatoid factor and anti-cyclic citrullinated peptide antibody (anti-CCP), further screening of such seronegative subjects may be suspended.

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-105 capsules and matching placebo capsules and upadacitinib tablets and matching placebo tablets provided for the study will be identical in appearance.

In the event of a medical situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie Therapeutic Area Medical Director prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie Therapeutic Area Medical Director, the Investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available to the Investigator. If the IRT system is unavailable, unblinding may occur by contacting EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/help-desk/. In the event that the blind is broken before notification to the AbbVie Therapeutic Area Medical Director, we request that the AbbVie Therapeutic Area Medical Director be notified within 24 hours of the blind being broken.

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 the IEC/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 Complaints

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 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 AEs are reported, then the following supplemental report(s) must be completed.

Table 3. AEs Requiring Supplemental Reports

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
Renal impairment **Renal dysfunction** **Renal failure** **Serum creatinine > 2.0 mg/dL**	Renal eCRF
Herpes zoster infection	Herpes zoster eCRF
Thrombotic events **Non-cardiac, non-central nervous system (CNS) embolic or thrombotic event (i.e., deep vein thrombosis or pulmonary embolism)**	Embolic and Thrombotic (non-cardiac, non-CNS) eCRF

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

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

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

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs 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.

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

Adverse Events of Special Interest

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

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

- Embolic and thrombotic events (non-cardiac, non-CNS).

Adverse Event Severity and Relationship to Study Drug

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

If no grading criteria are provided for the reported event, then the event should be as follows:

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Severe (Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
- Life-threatening (Grade 4): urgent intervention indicated or death related to AE.

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).

Information regarding the pregnancy and the outcome will be collected.

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 4 and in the Operations Manual.

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

For subjects who discontinue study drug but continue 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.

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 an 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 or experience hepatitis B reactivation must be discontinued from study drug. To further monitor subjects for serious infections, subjects will complete at-home weekly temperature monitoring. If above 100.5 degrees Fahrenheit (38 degrees Celsius), subject should inform their study doctor to assess the need for further evaluation.

Canada only: Investigators should be advised to follow local public health guidelines in order to prevent subjects enrolled in these trials from acquiring TB.

Serious Gastrointestinal Events: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued from study drug.

Cardiovascular Events (MACE): Subjects presenting with potential cardiovascular events should be carefully monitored. These events will be reviewed and adjudicated by the independent CAC.

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

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

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values

are described in Table 4 and may require an appropriate supplemental eCRF be completed. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 4, the repeat testing must occur as soon as possible.

Table 4. 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 a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1000 cells/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its baseline value. • Discontinue study drug if confirmed < 500 cells/µL by repeat testing with new sample.
Absolute lymphocyte counts (ALC)	• If confirmed < 500 cells/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its baseline value.
Total white blood cell count	• If confirmed < 2,500 cells/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its baseline value.
Platelet count	• If confirmed < 50,000 platelets/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

Laboratory Parameter	Toxicity Management Guideline

Aspartate transaminase (AST) or alanine transaminase (ALT)	• Interrupt study drug immediately if confirmed ALT or AST > 3 × upper limit of normal (ULN) by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5.
	  • INR will only need to be measured in subjects with ALT or AST > 3 × ULN by the central lab. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
	• Interrupt study drug immediately if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• Interrupt study drug immediately if confirmed ALT or AST > 8 × ULN by repeat testing with new sample.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. 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.
	For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.
	• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within one week:
	  • 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 in these subjects will require immediate interruption of study drug and a hepatologist consultation should occur within one week for recommendation regarding subsequent treatment.

Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × baseline value and ≤ ULN. • If confirmed serum creatinine ≥ 2 mg/dL interrupt study drug, and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.

Laboratory Parameter	Toxicity Management Guideline
Creatine Phosphokinase (CPK)	• If confirmed CPK value ≥ 4 × ULN (if symptomatic or asymptomatic), complete supplemental CPK eCRF. • If confirmed CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug, complete supplemental CPK eCRF, and contact AbbVie Therapeutic Area Medical Director.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the final (Week 12) database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA). The final analysis will be conducted by AbbVie Statistics group at the final database lock, and the unblinded interim safety reviews will be conducted by the DMC at pre-specified time points as described in Section 7.5, Interim Analysis.

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of randomized study drug. The FAS will be used for all efficacy and baseline analyses. Subjects will be grouped according to treatment as randomized.

The Safety Set consists of all enrolled subjects who received at least 1 dose of study drug. Safety analyses are based on treatments actually received.

7.3 Statistical Analyses for Efficacy

Primary Endpoint Analysis

The primary endpoint is change from baseline in DAS28-CRP at Week 12.

The first primary analysis is to test the superiority of ABBV-599 compared to placebo at Week 12.

The second primary analysis is to test a pre-specified set of dose-response models (detailed in the SAP) among ABBV-105 dose groups and the placebo group at Week 12 using the Multiple Comparison Procedure – Modeling (MCP-Mod) method.[9,10]

Hypothesis testing in the primary analyses will be performed in a ranked fashion based on one-sided significance level of $\alpha = 0.05$. The other analysis for the primary endpoint includes testing the superiority of ABBV-599 compared to each ABBV-105 dose group, as well as to upadacitinib. Additionally, each ABBV-105 group will be compared vs placebo group. All tests will be performed as

pairwise comparison at one-sided statistical significance level $\alpha = 0.05$. The listing of these analyses is as follows:

- ABBV-599 vs placebo
- ABBV-105 dose response
- ABBV-599 vs each ABBV-105 dose
- Each ABBV-105 dose vs placebo
- ABBV-599 vs upadacitinib

In the analyses, the treatment mean will be estimated using least squares (LS) mean from Mixed-Effect Model Repeated Measurements (MMRM) method. One MMRM model including all treatment groups up to visit Week 12 data modeling will be used. Comparable historical placebo and upadacitinib data will be used to enhance the statistical power in relevant comparison analyses, which are detailed in the SAP.

Secondary Endpoints Analysis

Continuous efficacy variables will be analyzed using an MMRM method. It will be used for primary inference purpose. 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 and as observed (AO) analyses will be used for sensitivity analysis for selected endpoints.

Missing Data Imputation Definition

Non-Responder Imputation: An NRI approach will categorize any subject who has missing value for categorical variables at a specific visit as non-responder for that visit. In addition, subjects who prematurely discontinue from study drug will be considered as non-responders for all subsequent visits after discontinuation.

As Observed: AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. Regardless of treatment switching or premature discontinuation of study drug, all observed data will be used in the analysis.

Observed Case (OC): OC analysis will not impute values for missing evaluations and, thus, a subject who does not have an evaluation on a scheduled visit will be excluded from OC analysis for that visit. In addition, the OC analysis will not use values after premature discontinuation of study drug.

Mixed-Effect Model Repeated Measurements (MMRM): MMRM analysis will be conducted using mixed-effect model with OC analysis. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors, and the continuous fixed covariate of baseline measurement. An unstructured variance covariance matrix will be used. The parameter estimations are based on the assumption of data being missing at random and using the method of restricted maximum likelihood (REML).

7.4 Statistical Analyses for Safety

All safety analyses will be performed in the safety populations.

Pre-treatment AEs will be summarized separately.

All treatment-emergent adverse events (TEAEs), SAEs, AEs leading to discontinuation, and AESI will be collected during the study. A TEAE is defined as an event with onset or worsening after the first study dose of study drug and within 30 days after the last dose of study drug administration. The number and percentages of subjects experiencing TEAEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-year) of SAEs, deaths, AEs leading to discontinuation, and AESI will be provided as well. For selected laboratory and vital signs parameters, mean change from baseline and percentage of subject with evaluations meeting pre-defined criteria for Potentially Clinically Important values will be summarized.

7.5 Interim Analysis

An unblinded interim analysis to review safety will be conducted by an independent internal DMC at 3 time points and ad hoc as needed: when approximately 50% of subjects have completed Week 4 evaluation, when approximately 80% of subjects have completed Week 4 evaluation, and when approximately 80% of subjects have completed Week 12 evaluation. The sponsor, study sites and subjects will remain blinded for the duration of the study. The details will be given in the DMC charter or related SAP.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, and relevant safety data to be assessed.

7.6 Sample Size Estimation

The planned total sample size is 240. Forty patients per arm of ABBV-105 can provide approximately 83% power to detect a –0.88 difference in DAS28 (CRP) change from baseline for ABBV-105 vs 20 placebo patients combined with 20 borrowed historical placebo subjects (assuming a placebo mean change from baseline: –0.77, and ABBV-105: –1.65 with common standard deviation [SD] = 1.5) using two group t-test with a 0.05 one-sided significance level. It can provide minimum of 85% power to detect a dose-response model for ABBV-105 and combined placebo from 6 candidate models: Linear ($\delta = 0.01$), EMax (ED50 = 5 mg), Exponential ($\delta = 20$), Logistic (ED50 = 5 mg, $\delta = 10$), SigEMax (ED50 = 5 mg, h = 2), and Quadratic ($\delta = -0.01$) using MCP-Mod with a 0.05 one-sided significant level. In the event that placebo variability precludes historic borrowing, comparison using only the in-study 20 placebo patients is still estimated to provide 68% power for pairwise comparison of ABBV-105 vs placebo or a minimum of 70% power in detecting a dose-response model for ABBV-105 and placebo.

The planned sample size of 60 patients treated with ABBV-599 provides about 94% power to detect a –1.0 increase in DAS28 (CRP) LS mean change from baseline for ABBV-599 vs the group of 40 patients treated with ABBV-105 (assuming ABBV-105 mean change from baseline: –1.65 and ABBV-599: –2.65

with common SD = 1.5) using two group t-test with one-sided α = 0.05 significant level. The sample size of 60 for ABBV-599 vs 40 for placebo is over powered due to the necessary power for ABBV-105 over placebo.

The 60 patients for ABBV-599 vs 40 for upadacitinib could extend around 0.5 from observed difference in mean change from baseline for a two-sided 90% confidence interval assuming the common SD = 1.5. Supposing the difference for ABBV-599 vs upadacitinib is –0.45, the 90% confidence interval of (–0.95, 0.05) could be detected with given same size.

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

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

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug, and study protocol.

The end-of-study is defined as the date of the last subject's last visit.

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACR	American College of Rheumatology
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte counts
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-CCP	anti-cyclic citrullinated peptide antibody
AO	as observed
AST	aspartate transaminase
bDMARD-IR	biologic disease-modifying anti-rheumatic drugs – inadequate response
bDMARD	biologic disease-modifying anti-rheumatic drug
BP	blood pressure
Btk	Bruton's tyrosine kinase
CAC	Cardiovascular Adjudication Committee
CDAI	clinical disease activity index
CL/F	apparent clearance or apparent oral clearance
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPK	creatine phosphokinase
CR	clinical remission
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying anti-rheumatic drug
CVA	cerebrovascular accident
CYP	cytochrome P450
CXR	chest x-ray
DAS	disease activity score
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis

ECG	electrocardiogram
eCRF	electronic case report form
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
HAQ-DI	Health Assessment Questionnaire Disability Index
HBc Ab	hepatitis B core antibody
HBs Ag	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	anti-HCV antibody
Hgb	hemoglobin
HIV	human immunodeficiency virus
HIV Ab	HIV antibody
hsCRP	high-sensitivity C-reactive protein
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus kinase
LDA	low disease activity
LS	least squares
LTE	long-term extension
MACE	major adverse cardiovascular event
MCID	minimal clinically important difference
MCP-Mod	Multiple Comparison Procedure – Modeling

MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measurements
MTX	methotrexate
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drug
OC	observed case
PCR	polymerase chain reaction
PD	premature discontinuation
PE	pulmonary embolism
PhGA	Physician's Global Assessment of Disease Activity
PtGA	Patient's Global Assessment of Disease Activity
PK	Pharmacokinetic(s)
PPD	purified protein derivative
QD	once daily
QTc	corrected QT
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
PRN	as needed (pro re nata)
RA	rheumatoid arthritis
REML	restricted maximum likelihood
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDAI	simplified disease activity index
SUSAR	suspected unexpected serious adverse reactions
SJC	swollen joint count
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TBNKM	T lymphocytes, B lymphocytes, natural killer lymphocytes, and monocytes
TEAE	treatment-emergent adverse event
TJC	tender joint count
ULN	upper limit of normal

VAS	visual analog scale
V_{ss}/F	apparent volume of distribution at steady state
WBC	white blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-063: A Phase 2 Study to Investigate the Safety and Efficacy of ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599 Combination) with a Background of Conventional Synthetic DMARDs in Subjects with Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs

Protocol Date: 15 October 2019

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]		Immunology
		Clinical Program Development
		Study Project Management
		Medical Writing
		Data and Statistical Sciences
		Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The individual activities are described in detail in the Operations Manual.

Study Activities Table

	Screening (Day −35 to D −1)	Baseline	Week 2	Week 4	Week 8	Week 12/ PD	30-Day Follow-Up Visit[a]
INTERVIEWS & QUESTIONNAIRES							
Subject information and informed consent	✓						
Eligibility criteria	✓	✓					
Medical and surgical history	✓						
Drug and alcohol screen (urine)	✓						
Adverse events (AE) and AE of special interest (AESI) assessment		✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓
Latent tuberculosis (TB) risk assessment form	✓						
Patient Questionnaires: • Patient Global Assessment of Disease Activity (PtGA) • Pain Visual Analog Scale (VAS) • Health Assessment Questionnaire Disability Index (HAQ-DI) • Morning Stiffness		✓	✓	✓	✓	✓	
Physician Global Assessment (PhGA)		✓	✓	✓	✓	✓	
LOCAL LABS & EXAMS							
12-lead electrocardiogram (ECG)	✓		✓	✓	✓	✓	
Height and body circumference	✓						
Weight	✓	✓				✓	
Vital signs	✓	✓	✓	✓	✓	✓	
Physical exam	✓	✓	✓	✓	✓	✓	
Tender Joint Count (TJC)68/Swollen Joint Count (SJC)66	✓	✓	✓	✓	✓	✓	
Local urine pregnancy test		✓	✓	✓	✓	✓	
Chest x-ray (CXR)	✓						
Erythrocyte sedimentation rate (ESR)	✓	✓	✓	✓	✓	✓	

	Screening (Day −35 to D −1)	Baseline	Week 2	Week 4	Week 8	Week 12/ PD	30-Day Follow-Up Visit[a]
CENTRAL LABS							
Serum pregnancy test at central lab	✓						
Follicle stimulating hormone (FSH) if ≤ 55 years and no menses for 12 or more months without an alternative medical cause	✓						
Rheumatoid factor and anti-cyclic citrullinated peptide antibody (anti-CCP)	✓						
Central Laboratory Tests: • High-sensitivity C-reactive protein (hsCRP) • Blood chemistry • Hematology • Urinalysis	✓	✓	✓	✓	✓	✓	
Cotinine lab measurement		✓	✓	✓	✓	✓	
QuantiFERON-TB Gold test (and/or local PPD skin test) or T SPOT.*TB* test[b]	✓						
HIV Testing (if not prohibited by local regulations)	✓						
HBs Ag, HBc Ab, HCV Ab	✓						
Blood sample for ABBV-105 and upadacitinib pharmacokinetic (PK) analysis		✓		✓	✓	✓	
Biomarker samples: whole blood for B cell subsets and T lymphocytes, B lymphocytes, natural killer lymphocytes, and monocytes (TBNKM)		✓[c]		✓		✓	
Biomarkers samples: whole blood for Btk occupancy analysis (only select # of sites and subjects in the US)		✓[c]		✓		✓	
Biomarker samples: whole blood for serum, plasma, DNA, and RNA		✓[c]		✓		✓	
TREATMENT							
Randomization/drug assignment		✓					
Dispense subject dosing diary and at-home temperature monitoring log		✓					
Dispense study drug		✓		✓	✓		
Review study drug return and perform drug reconciliation			✓	✓	✓	✓	
Review at-home temperature monitoring log and reminder to subjects to conduct their weekly at-home temperature monitoring[d]		✓	✓	✓	✓	✓	

a. Applies only to those subjects who do not enter LTE Study M16-763.

b. As available and if compliant with local TB guidelines in Canada only.

c. Pre-dose collection.

d. As described in Section 6.2.

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. Temporomandibular	0	1	0	1	9	NA	0	1	0	1	9	NA
2. Sternoclavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
3. Acromio-clavicular	0	1	0	1	9	NA	0	1	0	1	9	NA
4. Shoulder	0	1	0	1	9	NA	0	1	0	1	9	NA
5. Elbow	0	1	0	1	9	NA	0	1	0	1	9	NA
6. Wrist	0	1	0	1	9	NA	0	1	0	1	9	NA
7. Metacarpophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA
8. Metacarpophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
9. Metacarpophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
10. Metacarpophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
11. Metacarpophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
12. Thumb Interphalangeal	0	1	0	1	9	NA	0	1	0	1	9	NA
13. Prox. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
14. Prox. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
15. Prox. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
16. Prox. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
17. Distal Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
18. Distal Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
19. Distal Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
20. Distal Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
21. Hip	0	1	--	--	9	NA	0	1	--	--	9	NA
22. Knee	0	1	0	1	9	NA	0	1	0	1	9	NA
23. Ankle	0	1	0	1	9	NA	0	1	0	1	9	NA
24. Tarsus	0	1	0	1	9	NA	0	1	0	1	9	NA
25. Metatarsophalangeal I	0	1	0	1	9	NA	0	1	0	1	9	NA

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	
26. Metatarsophalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
27. Metatarsophalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
28. Metatarsophalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
29. Metatarsophalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
30. Great Toe/Hallux	0	1	0	1	9	NA	0	1	0	1	9	NA
31. Interphalangeal II	0	1	0	1	9	NA	0	1	0	1	9	NA
32. Interphalangeal III	0	1	0	1	9	NA	0	1	0	1	9	NA
33. Interphalangeal IV	0	1	0	1	9	NA	0	1	0	1	9	NA
34. Interphalangeal V	0	1	0	1	9	NA	0	1	0	1	9	NA
TOTAL Joint Count												

APPENDIX F. RHEUMATOLOGY COMMON TOXICITY CRITERIA V.2.0 EXAMPLE

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

Rheumatology Common Toxicity Criteria v.2.0 **Based on Woodworth TG, et al. Standardizing assessment of adverse effects in rheumatology clinical trials II. Status of OMERACT Drug Safety Working Group May 2006: OMERACT 8. Standardizing Assessment and Reporting of Adverse Effects in Rheumatology Clinical Trials: Enabling Description of Comparative Safety Profiles for 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 Hospitalised > 24 hr Study drug discontinued
A. Allergic/Immunologic				
A1. Allergic reaction/ hypersensitivity (includes drug fever)	Transient rash: drug fever < 38°C: transient, asymptomatic bronchospasm	Generalised urticaria responsive to meds; or drug fever > 38°C, or reversible bronchospasm	Symptomatic bronchospasm requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/pharyngeal oedema, requiring resuscitation
A2. Autoimmune reaction	Seriologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g., vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g., transient colitis or anaemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med. required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g., oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy

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

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

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

E. Ear/Nose/Throat (continued)				
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis)	Intermittent hoarseness, able to vocalise	Persistent hoarseness, able to vocalise	Whispered speech, slow return of ability to vocalise	Unable to vocalize for extended
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition
F. Eye/Ophthalmologic				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA
F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight
F5. Vision changes (e.g., blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophtalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight

G. Gastrointestinal				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support	Requires hospitalization for nutritional support
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2 – 3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4 – 6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g., incontinence, severe cramping, partial response to treatment.	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤ 2 units needed; responds to treatment	Haematemesis, transfusion 3 – 4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation
G6. Haematochezia (rectal bleeding)	Haemorrhodial, asymptomatic, no transfusion	Symptomatic, transfusion ≤ 2 units, reversible	Recurrent, transfusion > 3 – 4 units	> 4 units, hypotension, requiring hospitalization
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent > 2 wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma
G8. Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management
G9. Pancreatitis	Anylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatitic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required.

H. Musculoskeletal				
H1. Avascular necrosis	Asymptomatic MRI changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalisation required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, responds to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non-narcotic); minor effects on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds
I. Neuropsychiatric				
I1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms, partial or no response to meds, limits daily function	Suicidal ideation or danger to self
I2. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischaemic events	Cerebrovascular vascular accident with permanent disability
I3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with routine daily routine	Debilitating/disabling and permanent; toxic psychosis
I4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obundation, stupor	Coma
I5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings or organic cause	NA
I6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA
I7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged interfering with relationship	NA
I8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis

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 medication	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
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
L. Chemistry				
L1. Hypercalcaemia (mg/dl)	1.1 × ULN – 11.5	11.6 – 12.5	12.6 – 13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycemia (mg/dl) Fasting	140 – 160	161 – 250	251 – 500	> 500, or associated with ketoacidosis
L3. Hyperkalaemia (mg/dl)	5.5 – 5.9	6.0 – 6.4	6.5 – 7.0 or any ECG change	> 7.0 or any arrhythmia
L5. Hypocalcaemia (mg/dl)	0.9 × LLN – 7.8	7.7 – 7.0	6.9 – 6.5; or associated with symptoms	< 6.5 or occurrence of tetany
L6. Hypoglycemia (mg/dl)	55 – 64 (no symptoms)	40 – 54 (or symptoms present)	30 – 39 (symptoms impair function)	< 30 or coma
L7. Hyponatraemia (mg/dl)	--	125 – 129	120 – 124	< 120
L8. Hypokalaemia (mg/dl)	--	3.0 – 3.4	2.5 – 2.9	< 2.5

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

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

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	25 May 2018
Version 2.0	11 July 2018
Version 3.0	05 October 2018
Version 4.0	11 March 2019

The purpose of this Amendment is to update the following:

Protocol

- Update Section 4.1, Section 7.1, and Section 7.5 to remove interim efficacy analysis wording.

  Rationale: *The interim efficacy analysis is removed as the study has enrolled more slowly than anticipated and, as a result, the interim efficacy analysis would not save enough time to be worthwhile in terms of designing the next Phase of the ABBV-599 Rheumatoid Arthritis Program.*

- Update Sponsor/Emergency Medical Contact info and Appendix C, List of Protocol Signatories.

  Rationale: *Revised due to personnel change.*

- Minor typographical corrections made for clarity.