abbvie

Protocol for Study M20-466

Moderate to Severe Rheumatoid Arthritis: A Phase 2b, Dose-Ranging, Safety and Efficacy Study of ABBV-154

VERSION:	2.0	DATE:	12 April 2022
SPONSOR:	AbbVie*	PLANNED NUMBER OF SITES:	270
ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-154	EudraCT:	2020-005303-39

FULL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to Biologic and/or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs (b/tsDMARDs)

Incorporating Versions 1.0, 1.1 (Japan Only), 1.2 (United Kingdom Only), 2.0 and Administrative Change 1

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted] MD, PhD
AbbVie Inc.
1 N. Waukegan Road
North Chicago, IL 60064
Office/Mobile: [redacted]
Fax:
Email:

EMERGENCY 24 hour Number: +1 973-784-6402

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix G).

abbvie

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to Biologic and/or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs (b/tsDMARDs)	
Background and Rationale:	Tumor necrosis factor (TNF) antagonists are effective therapies with established safety profiles in patients with immune-mediated inflammatory diseases, including rheumatoid arthritis (RA). Nevertheless, there remains an unmet clinical need for improved therapies as even biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in combination with methotrexate (MTX) fail to achieve optimal disease control in some patients. Therefore, there is a particular need for improved therapies in refractory RA patients. Glucocorticoids are potent drugs for treating many inflammatory diseases, including RA. However, the full efficacy of glucocorticoid therapy is limited with existing agents due to systemic side effects. ABBV- 154 is an anti-TNF antibody-drug conjugate (ADC) composed of adalimumab (the active component of Humira®) conjugated to phosphorylated A-1677770, a proprietary glucocorticoid receptor modulator (GRM) via an [redacted] linker. The A-1677770 GRM is a synthetic glucocorticoid receptor agonist with a steroid backbone, optimized to provide the widest therapeutic window in-vivo between anti-inflammatory effects and systemic glucocorticoid effects. Therefore, adalimumab/GRM ADC has the potential to deliver an anti-inflammatory payload to activated immune cells that express transmembrane TNF and minimize systemic exposure to the free GRM payload. Thus, based on its mechanism of action, ABBV-154 has the potential to achieve transformational efficacy relative to adalimumab while reducing side effects caused by systemic exposure to glucocorticoids.
Objective(s) and Endpoint(s):	Primary Objective: To assess the safety, tolerability, and efficacy of ABBV-154 administered every other week (eow) and every 4 weeks (e4w) subcutaneously (SC) vs placebo in subjects with moderately to severely active RA with inadequate response to at least one prior b/tsDMARD. Secondary Objective: To assess the pharmacokinetics (PK), pharmacodynamics, and immunogenicity of ABBV-154. Primary Endpoint: Achievement of 50% improvement as measured by American College of Rheumatology response criteria (ACR50) at Week 12. Secondary Endpoints: (all measured at Week 12) • Change in Disease Activity Score (DAS) 28 (CRP) from Baseline; • Change in Clinical Disease Activity Index (CDAI) from Baseline; • Achievement of ACR20;

	• Achievement of ACR70; • Achievement of Low Disease Activity (LDA) defined by DAS28 (CRP) ≤ 3.2; • Achievement of LDA defined by CDAI ≤ 10; • Achievement of clinical remission defined by DAS28 (CRP) < 2.6; • Achievement of clinical remission defined by CDAI ≤ 2.8; and • Change in Health Assessment Questionnaire Disability Index (HAQ-DI) from Baseline
Investigator(s):	Multicenter
Study Site(s):	Approximately 270 sites: Australia, Austria, Canada, Czechia, France, Germany, Greece, Hungry, Israel, Italy, Japan, Netherlands, New Zealand, Poland, Russia, Slovakia, South Korea, Spain, Taiwan, Turkey, Ukraine, United Kingdom, United States (including Puerto Rico)
Study Population and Number of Subjects to be Enrolled:	425 adults with moderate to severe RA receiving MTX and prior inadequate response to b/tsDMARDs
Investigational Plan:	This is a randomized, double-blind, Phase 2b dose-ranging study with a 12-week Placebo-Controlled Period, a 66-week Double Blind Long-Term Extension (LTE) Period, and a 104-week LTE Period in adults with moderately to severely active RA on background MTX, who have had an inadequate response to at least one b/tsDMARD. The study is comprised of a 35-day Screening Period, a 12-week Double-Blind, Placebo-Controlled Period, a Double-Blind LTE Period 1 of 66 weeks, a LTE Period 2 of 104 weeks, and a 70-day Follow-up Period after the last dose of study drug. **Placebo-Controlled Period:** 425 subjects will be randomized to 5 treatment groups in a 1:1:1:1:1 ratio to receive blinded ABBV-154 at a dose of 40 mg, 150 mg, or 340 mg, SC eow; 340 mg SC e4w; or placebo SC eow for 12 weeks. Randomization will be stratified by baseline glucocorticoid use (yes/no); number of prior failed b/tsDMARDs (1; 2 or more), prior anti-TNF failure (yes/no) and if yes further stratification by prior adalimumab use (yes/no). **Double-Blind LTE Period 1:** At the end of the 12-week Placebo-Controlled Period, subjects in the placebo group will be re-randomized in a 1:1 ratio to receive ABBV-154 150 mg or 340 mg SC eow. Re-randomization will be stratified by baseline glucocorticoid use (yes/no) and prior adalimumab use (yes/no). Subjects from the other dose groups will continue with their respective dose and dosing regimen. **LTE Period 2:** Subjects that completed the 66-week LTE Period 1 will be invited to participate in the 104-week LTE Period 2. The primary analysis will be conducted after all ongoing subjects have completed Week 12 or have withdrawn from the study. Additional analyses may be conducted as needed. A final analysis will be conducted after all subjects have completed LTE Period 2 and a safety Follow-up Visit, 70 days after the last dose of study drug, or have withdrawn from the study. To maintain integrity of the trial, study sites and subjects will remain blinded until all subjects have either

	completed the last visit of LTE Period 1 or have withdrawn from the study.

Key Eligibility Criteria:	• Adults 18 – 75 years of age at Screening;
	• Clinical diagnosis of RA with symptoms onset ≥ 3 months prior to Screening and fulfillment of the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA.
	• Subject has ≥ 6 swollen joints (based on 66 joint count) and ≥ 6 tender joints (based on 68 joint count) at Screening and Baseline.
	• Subject must have had inadequate response to at least one of the following prior b/tsDMARD treatments for RA (or corresponding biosimilar):
	  • Tumor necrosis factor inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
	  • Interleukin-1 receptor inhibitors: anakinra
	  • Interleukin-6 receptor inhibitors: tocilizumab, sarilumab
	  • CD20-directed cytolytic antibodies: rituximab
	  • T cell costimulation modulators: abatacept
	  • Janus Kinase inhibitors: baricitinib, filgotinib, peficitinib, tofacitinib, upadacitinib
	  • Investigational drug with positive efficacy data available from confirmatory trials, as agreed with the AbbVie TA MD
	• Subjects may not have had inadequate response to more than 3 b/tsDMARDs and not more than 2 different mode of actions.
	• Inadequate response is defined by at least one of the following criteria:
	  a. Subject did not show an adequate response to b/tsDMARDs after continuous treatment of ≥ 3 months; or
	  b. Subject discontinued b/tsDMARDs due to intolerability or toxicity, irrespective of treatment duration. Subject must not have discontinued prior adalimumab therapy due to intolerability or toxicity.
	  Note: b/tsDMARDs that were discontinued due to other reasons unrelated to inadequate response (e.g., good response or non-medical reasons including insurance/financial issues, trial ended, etc.) will not be accepted to fulfill eligibility criteria.
	• Subjects must be on stable dose of MTX (≥ 4 weeks) before the first dose of study drug.

Study Drug and Duration of Treatment:	Double-Blind, Placebo-Controlled Period: ABBV-154 40 mg, 150 mg, 340 mg SC eow; 340 mg SC e4w or placebo SC eow for 12 weeks. Double-Blind LTE Period 1: At the end of Week 12, subjects initially on placebo will be re-randomized 1:1 to receive ABBV-154 150 mg or

	ABBV-154 340 mg SC eow. Other subjects will remain on their previous dose and dosing regimen of ABBV-154. The duration of this period is 66 weeks. LTE Period 2: subjects that completed the 66-week LTE Period 1 will be invited to participate in the 104-week LTE Period 2. All subjects will remain on their previous dose and dosing regimen of ABBV-154.
Date of Protocol Synopsis:	12 April 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Evidence suggests that tumor necrosis factor (TNF) antagonists reduce the signs and symptoms of disease by reducing inflammation and limiting the progression of tissue destruction and are considered effective therapies with established safety profiles in patients with immune-mediated inflammatory diseases, including rheumatoid arthritis (RA). Nevertheless, there remains an unmet clinical need for improved therapies as even biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in combination with methotrexate (MTX) fail to achieve optimal disease control in some patients. Therefore, there is a particular need for improved therapies in refractory RA patients.

Glucocorticoids are potent drugs for treating many inflammatory diseases. In RA, glucocorticoids such as prednisone are highly effective at reducing inflammation, fatigue, radiographic progression, and relieving pain. However, the administration of glucocorticoids is limited due to their long-term side effect profile including (but not limited to) hypothalamic-pituitary-adrenal axis (HPA) suppression, osteoporosis, hyperglycemia, glaucoma, and skin atrophy.[1] Thus, the full efficacy of glucocorticoid therapy is often limited with existing agents due to systemic side effects.

AbbVie is developing ABBV-154, an anti-TNF antibody-drug-conjugate (ADC) composed of adalimumab (the active component of Humira®) conjugated to phosphorylated A-1677770, a proprietary, glucocorticoid receptor modulator (GRM) via an [redacted] linker. The A-1677770 GRM is a synthetic glucocorticoid receptor agonist with a steroid backbone, optimized to provide the widest therapeutic window in-vivo between anti-inflammatory effects and systemic glucocorticoid effects. Therefore, ABBV-154 has the potential to deliver an anti-inflammatory payload to activated immune cells that express transmembrane TNF and minimize systemic exposure to the free payload GRM. Thus, ABBV-154 (adalimumab/GRM ADC) has the potential to achieve transformational efficacy relative to adalimumab while reducing side effects caused by systemic exposure to glucocorticoids.

2.2 Benefits and Risks to Subjects

The clinical efficacy of TNF inhibitors and glucocorticoids in the treatment of RA is well established. Based on the totality of the evidence from preclinical and clinical data, ABBV-154 is expected to demonstrate therapeutic benefit in the treatment of RA with an acceptable benefit/risk profile.

Medical review of the safety data from the Phase 1, single ascending dose study did not identify any safety risks in the healthy volunteer population (including Japanese and Chinese subjects). For further details, please see the ABBV-154 Investigator's Brochure.[2]

In clinical settings, TNF antagonists and glucocorticoids have been associated with increased risk for serious infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens. Patients with a recent history of these events will be excluded from the study. Other known adverse events (AE) for glucocorticoids include hypertension, HPA suppression, decreased bone-

formation, diabetes, and cataracts. Signs of infection, blood pressure changes, blood glucose levels, HPA axis suppression, and bone mineral density will be closely monitored during the study.

TNF antagonists have also been associated with an increased risk for serious allergic reactions, including anaphylaxis; infusion reactions; malignancy (including nonmelanoma skin cancer, lymphoma, and leukemia); worsening or new onset heart failure; and rarely hepatitis B virus (HBV) reactivation, central nervous system events, demyelinating disease, pancytopenia (including aplastic anemia, and lupus-like syndrome). Patients with a history of these events will be excluded from the study. Signs and symptoms of these events will be closely monitored.

The safety profile specific to the adalimumab component of ABBV-154 is well-established for marketed doses. In addition, adalimumab has been studied at doses up to 10 mg/kg IV, which is higher than the doses planned in this study, with a safety profile consistent to Humira® product labeling. Potential risks will be minimized through the selection of appropriate study subjects defined by the eligibility criteria and subject safety will be monitored by an unblinded independent data monitoring committee (DMC) and regular blinded review of safety data by the study team. In addition, guidance for toxicity management and stopping rules are provided to ensure subject safety.

Based on the totality of the data, ABBV-154 is expected to demonstrate therapeutic benefit in the treatment of RA with an acceptable benefit-risk profile for development in the treatment of this disease.

In view of the coronavirus pandemic 2019 (COVID-19), the benefit-risk profile of various immunomodulatory therapies on COVID-19 are being evaluated. Currently, the effects of ABBV-154 on the course of COVID-19 are not well defined.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary Objective

The primary objective is to assess the safety, tolerability, and efficacy of ABBV-154 vs. placebo on background MTX for the treatment of subjects with moderately to severely active RA who have had an inadequate response to at least one prior b/tsDMARD.

The primary efficacy objective of the study is to demonstrate a higher rate of ACR50 after 12 weeks of treatment with ABBV-154 when compared to placebo in the Intent-to-Treat (ITT) Population (further described in Section 7.2), which consists of all randomized subjects who have received at least one dose of study drug. The hypothesis corresponding to the primary efficacy objective and endpoint is the proportion of subjects achieving ACR50 with ABBV-154 is greater than that with placebo at Week 12. The estimand for the primary endpoint is defined as the difference in the proportion of subjects that achieve ACR50 at Week 12, in each of the ABBV-154 dose groups compared with the placebo group in the ITT Population.

The secondary efficacy objectives of the study are to demonstrate higher efficacy of treatment with ABBV-154 when compared to placebo with respect to the secondary endpoints specified in Section 3.3; in the ITT Population. The estimands corresponding to the secondary efficacy objectives are:

- For each of the categorical secondary endpoints, the estimands corresponding to the secondary efficacy objectives are defined as follows: Difference in the proportion of subjects achieving the endpoint, in each of the ABBV-154 groups in comparison with the placebo group in the ITT Population.
- For each of the continuous secondary endpoints, the estimands corresponding to the secondary efficacy objectives are defined as follows: Difference in the mean change from baseline of the endpoint, in each of the ABBV-154 dose groups in comparison with the placebo group in the ITT Population.

Secondary Objective

The secondary objective is to assess the pharmacokinetics (PK), pharmacodynamics, and immunogenicity of ABBV-154.

3.2 Primary Endpoint

The primary endpoint is the achievement of ACR50 at Week 12.

3.3 Secondary Endpoints

All secondary endpoints are at Week 12.

- Change in Disease Activity Score (DAS) 28 (CRP) from Baseline;
- Change in Clinical Disease Activity Index (CDAI) from Baseline;
- Achievement of ACR 20;
- Achievement of ACR70;
- Achievement of low disease activity (LDA) defined by DAS28 (CRP) ≤ 3.2;
- Achievement of LDA defined by CDAI ≤ 10;
- Achievement of clinical remission (CR) defined by DAS28 (CRP) < 2.6;
- Achievement of CR defined by CDAI ≤ 2.8;
- Change in the Health Assessment Questionnaire Disability Index (HAQ-DI) from Baseline.

3.4 Additional Efficacy Endpoints

The primary endpoint and all secondary endpoints will be analyzed at all visits assessed other than Week 12. In addition, the following endpoints will be analyzed at all visits assessed.

- Change from Baseline in individual components of ACR
- Change from Baseline in simplified disease activity index (SDAI)
- Achievement of LDA defined as SDAI ≤ 11

- Achievement of CR defined as SDAI ≤ 3.3
- Achievement of Boolean remission based on a 28-joint count and defined as swollen joint count (SJC) ≤ 1, tender joint count (TJC) ≤ 1, high sensitivity C-reactive protein (hsCRP) ≤ 1 mg/dL, and Patient Global Assessment of Disease Activity ≤ 1
- Change from Baseline in PROMIS Pain Interference
- Change from Baseline in FLARE-RA

3.5 Safety Measures

1. Treatment-emergent adverse events, serious adverse events (SAEs), and AEs leading to discontinuation of the study drug;
2. Occurrence of potentially glucocorticoid related AEs; and
3. Potentially clinically significant laboratory, vital signs, and electrocardiogram (ECG) variables.

3.6 Pharmacokinetic and Immunogenicity Endpoints

Serum or plasma concentrations of the conjugated ADC, total antibody, free payload A-1677770 will be determined at Baseline (pre-dose) and at timepoints during the treatment period as specified in the Activity Schedule (Appendix E).

Development of anti-drug antibody (ADA) to ABBV-154 will be evaluated and if confirmed positive, titers will be measured. Samples that are confirmed positive may be further characterized in a validated neutralizing antibody (nAb) assay. Immunogenicity samples will be collected at Baseline (pre-dose) and at timepoints as specified in the Activity Schedule (Appendix E).

3.7 Biomarker Research Endpoints

The effect of the ADC compound on glucocorticoid-related endpoints will be assessed by blood samples collected at specified time points (Activity Schedule, Appendix E) throughout the study. The biomarkers to be analyzed include, but are not limited to:

- Neuroendocrine biomarkers (cortisol) and adrenocorticotropic hormone (ACTH)
- Bone formation (osteocalcin [OC], procollagen type 1 N-propeptide [P1NP]) and resorption (C-terminal telopeptide of type I collagen [CTX]) biomarkers
- Blood leukocytes subpopulations

Provision of these biospecimens for biomarker research is mandatory, but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples described in the protocol.

Additional optional biospecimens (whole blood for serum, plasma, peripheral blood mononuclear cells, RNA, and DNA) will be collected at specified time points (Activity Schedule, Appendix E) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Types of biomarkers may include nucleic acids, proteins, cell populations, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to soluble proteins, genomic transcripts, blood leukocyte populations, and genetic analysis to evaluate biomarker endpoints related to safety, disease state, and target pathway. Results from this optional biomarker research results may not be included in the clinical study report. Further details regarding the biomarker research collection time points are located in the Operations Manual, Appendix G, Section 3.9.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, Phase 2b, dose-ranging study with a 12-week Placebo-Controlled Period, a 66-week Double-Blind Long-Term Extension (LTE) Period 1, a 104-week LTE Period 2, and a 70-Day Follow-up Period in adults with moderately to severely active RA and on background MTX, who have had an inadequate response to b/tsDMARDs treatment.

Subjects will remain on a stable dose of MTX until Week 24 (unless qualifying rescue therapy as described in Section 5.4); thereafter MTX may be adjusted within the range of 7.5 – 25 mg/week. At Baseline, 425 subjects will be randomized to 5 treatment groups in a 1:1:1:1:1 ratio to receive ABBV-154 at either 40 mg, 150 mg, 340 mg, subcutaneously (SC) every other week (eow); 340 mg SC every 4 weeks (e4w); or placebo SC eow. Randomization will be stratified by Baseline glucocorticoid (yes/no); number of prior failed b/tsDMARDs (1; 2 or more); and prior anti-TNF failure (yes/no) and if yes further stratification by prior adalimumab use (yes/no). At the end of the Week 12 Visit, subjects previously on placebo will be re-randomized and will receive ABBV-154 150 mg SC eow or ABBV-154 340 mg SC eow. At re-randomization, subjects will be stratified by baseline glucocorticoid use (yes/no) and prior adalimumab use (yes/no). Subjects from the other dose groups will continue with their respective dose and dosing regimen. The enrollment for subjects with prior adalimumab use is capped at approximately 30% of the total enrolled subjects.

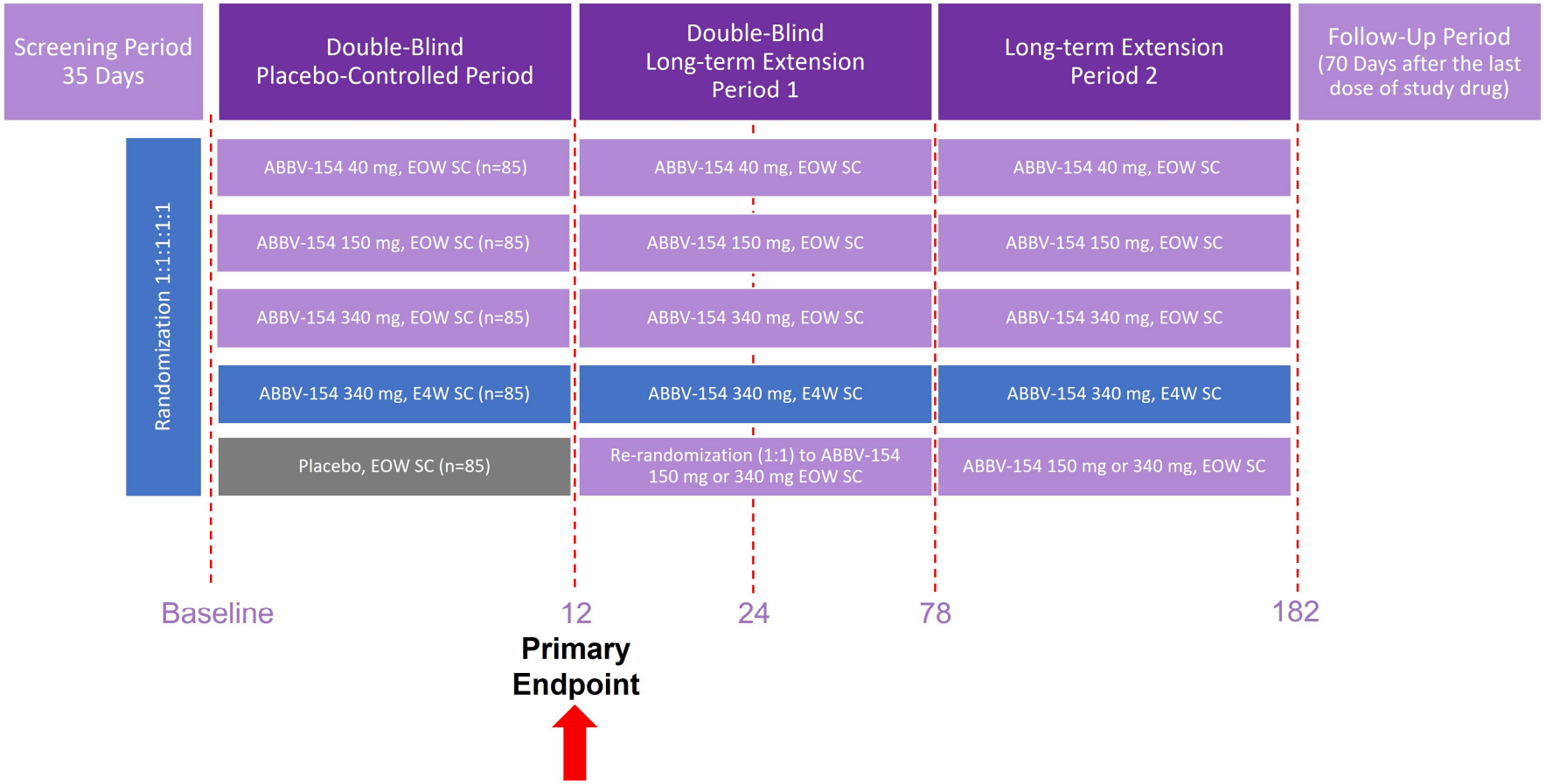
Systemic glucocorticoids (dose of ≤ 7.5 mg/d prednisone equivalent at Baseline) must be tapered off within 4 weeks of the start of study drug.

The Primary Analysis will be conducted after all ongoing subjects have completed Week 12 or have withdrawn from the study. After the Primary Analysis, additional analyses may be conducted as needed. A final analysis will be conducted after all subjects have completed LTE Period 2 and a safety follow-up visit or have withdrawn from the study. To maintain integrity of the trial, the study sites and subjects will remain blinded until all subjects have either completed the last visit of LTE Period 1 or have withdrawn from the study. The AbbVie study team will be unblinded to treatment assignment after the Primary Analysis.

The schematic of the study is shown in Figure 1.

Further details regarding study procedures are in the Operations Manual. See Section 5.1 for information regarding eligibility criteria.

Figure 1. Study Schematic



BL = Baseline; EOW = every other week; E4W = every 4 weeks; n = number of subjects; SC = subcutaneous

4.2 Discussion of Study Design

Choice of Control Group

Placebo has been selected as the appropriate control group to evaluate the primary efficacy endpoints as double-blind, placebo-controlled study designs are generally acknowledged as standard for unbiased estimates of treatment differences. There is no anticipated medical risk for subjects randomized to placebo with background concomitant MTX for 12 weeks.

Appropriateness of Measurements

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

Suitability of Subject Population

The mechanism of action of ABBV-154 has the potential to improve disease activity in RA subjects. While this is the first study to test ABBV-154 in RA subjects, safety results of ABBV-154 in healthy volunteers indicate no safety issues of concern and no dose limiting toxicity.

Selection of Doses in the Study

The dose selection in this study was informed by the safety, efficacy, PK, and pharmacodynamic results from a related ADC with the same mechanism of action (ABBV-3373) in a Phase 2a proof-of-concept study in bio-naïve RA patients on background MTX.

The 3 selected eow dosing regimens in this study (40 mg, 150 mg, and 340 mg SC) are reasonably separated across a wide dose range to cover the potential clinical efficacious doses and to enable a robust characterization of dose/exposure-response relationships for Phase 3 dose selection. In addition, the 340 mg SC e4w dose regimen was chosen to provide the optionality of an eow vs. e4w dosing frequency for future Phase 3 trials. All selected doses are within the range of single doses safely tested in the ABBV-154 First in Human Study (highest dose 600 mg intravenous) and are adequately covered by safety margins provided by chronic toxicology studies. Projected ABBV-154 and A-1677770 safety margins for the high dose of 340 mg SC eow are at least 24-fold and 10-fold, respectively, based on predicted ABBV-154 human exposures and the observed toxicokinetic data in the 26-week cynomolgus monkey study.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all the following criteria to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation. Additional information on screening (including re-screening) can be found in the Operations Manual, Appendix G.

Consent

- 1. Subject must be able to understand and willing to adhere to all protocol requirements and 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 and not more than 75 years of age at the time of Screening.
- 3. Body Mass Index (BMI) ≥ 18.0 to ≤ 39.9 kg/m^2 after rounding to the nearest tenth. BMI is calculated as weight in kg divided by the square of height measured in meters at the time of Screening.
- 4. **Laboratory values** must meet the following criteria within the Screening Period:
  - Serum aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) ≤ 2.5 × ULN;
  - Estimate glomerular filtration rate (eGFR) by simplified 4-variable Modification of Diet in Renal Disease formula ≥ 30 mL/min/1.73 m^2;
  - Absolute neutrophil count (ANC) ≥ 1,500/µL;
  - Absolute lymphocyte count (ALC) ≥ 800/µL;
  - Platelet count ≥ 75,000/µL;
  - Glycated hemoglobin (HbA1c ≤ 8.5%);
  - Serum potassium >3.0 mmol/L and < 5.5 mmol/L; and
  - Thyroid-stimulating hormone <10.0 mIU/L

Disease/RA Activity

- 5. Clinical diagnosis of RA with symptom onset for ≥ 3 months prior to Screening and fulfillment of the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA (Appendix B).
- 6. Subject must have: ≥ 6 swollen joints (based on 66 joint count) and ≥ 6 tender joints (based on 68 joint count) at Screening and Baseline.
- 7. Subject must have had inadequate response to at least one of the following prior b/tsDMARD treatments for RA (or corresponding biosimilar):
  - Tumor necrosis factor inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
  - Interleukin-1 receptor inhibitors: anakinra
  - Interleukin-6 receptor inhibitors: tocilizumab, sarilumab

- CD20-directed cytolytic antibodies: rituximab
- T cell costimulation modulators: abatacept
- Janus Kinase inhibitors: baricitinib, filgotinib, peficitinib, tofacitinib, upadacitinib
- Investigational drug with positive efficacy data available from confirmatory trials, as agreed with the AbbVie TA MD

8. Subjects may not have had inadequate response to more than 3 b/tsDMARDs and not more than 2 different mode of actions.

9. Inadequate response is defined as meeting at least one of the following criteria:

a. Subject did not show an adequate response to b/tsDMARDs after continuous treatment of ≥ 3 months; **or**

b. Subject discontinued b/tsDMARDs due to intolerability or toxicity, irrespective of treatment duration. Subject must not have discontinued prior adalimumab therapy due to intolerability or toxicity.

Note: b/tsDMARDs that were discontinued due to other reasons unrelated to inadequate response (good response or non-medical reasons including insurance/financial issues, trial ended, etc.) will not be accepted to fulfill eligibility criteria.

Subject History

10. Subject must not have a current or history of infection including:

- Chronic recurring infections (s) and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
- Active infection(s) requiring hospitalization or treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug administration;
- Active tuberculosis (TB) or meets TB exclusionary parameters (See specific requirements for TB testing and prophylaxis in the Operations Manual [Appendix G, Section 3.15]);
- Subjects in Japan only: positive result of beta-D-glucan (screening for Pneumocystis jirovecii infection) or two consecutive indeterminate results of beta-D-glucan during the Screening Period;
- Human Immunodeficiency virus (HIV) infection defined as confirmed positive anti-HIV antibody (HIV Ab) test;
- Confirmed COVID-19 infection: The Baseline visit must be at least 21 days from onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement of symptoms;
- Suspected COVID-19 infection: Subjects with signs/symptoms suggestive of COVID-19 infection, known exposure, or high-risk behavior, should undergo molecular (e.g., PCR) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days following potential exposure.

- 11. Subject must not have evidence of:
  - Hepatitis B virus (HBV): A positive test result for hepatis B surface antigen (HBsAg) or detectable HBV DNA PCR qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (and for Hepatitis B surface antibody [HBs Ab] positive subjects where mandated by local requirements).
  - Hepatitis C virus (HCV): A detectable HCV ribonucleic (RNA) acid in any subject with anti-HCV antibody (HCV Ab);
- 12. Subject must not have a history of the following medical diseases or disorders.
  - Suspected or confirmed adrenal insufficiency;
  - Hypothyroidism for which the subject is not receiving physiologic replacement therapy;
  - Moderate to severe congestive heart failure (New York Heart Association Class III or IV);
  - Uncontrolled hypertension defined as confirmed systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg at rest despite treatment;
  - Systemic lupus erythematosus, systemic sclerosis, inflammatory arthritis other than RA, inflammatory myopathies, or fibromyalgia;
  - Glaucoma, osteonecrosis or osteoporosis with high risk of fracture (e.g., T score ≤ -2.5 with history of fragility fracture);
  - Organ transplant which requires continued immunosuppression;
  - Demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease;
  - Any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix; and
  - History of any medical condition other than RA that is likely to require systemic glucocorticoid treatment during the study (e.g., asthma and chronic obstructive pulmonary disease per investigator judgement). Inhaled glucocorticoids are allowed for stable medical conditions but must be at stable dose ≥ 4 weeks prior to Baseline.
- 13. Subjects must not have a history of **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class. This includes anaphylactic reaction to any agent (e.g., food products or bee sting); or a reaction to any IgG containing product.
- 14. There must be no reason the investigator believes that the subject is an unsuitable candidate to participate in the study, receive study drug, or would be placed at risk by participating in the study.
- 15. Subjects must not have clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 12 months.

Contraception

- 16. Females of child-bearing potential must not have a **positive serum pregnancy test** at the Screening Visit and must have a negative urine pregnancy test at Baseline, prior to the first dose of study drug. Local practices may require a serum pregnancy test at Baseline. Subjects with a borderline serum pregnancy test at Screening must not have a clinical suspicion of pregnancy or other pathological cause of a borderline result and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).
- 17. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 70 days after the last dose of study drug. Local practices may require 2 methods of birth control. Refer to Section 5.2 for details on contraception. Female subjects of non-childbearing potential do not need to use birth control. For the United Kingdom (UK) only: Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is highly effective from Study Day 1 through at least 150 days after the last dose of study drug.
- 18. Females must not be **pregnant, or breastfeeding, or considering becoming pregnant** and may not donate eggs during the study or for approximately 70 days (150 days for UK only) after the last dose of study drug.
- 19. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through 70 days (150 days for UK only) after the last dose of study drug, to practice the protocol-specified contraception.
- 20. If male, must not be considering **fathering a child or donating sperm** during the study or for approximately 70 days (150 days for UK only) after the last dose of study drug.

Prior and Concomitant Medications

- 21. Subjects must be on stable dose of MTX (≥ 4 weeks oral or parenteral MTX ≥ 15 mg to ≤ 25 mg per week; or MTX ≥ 10 mg per week in subjects who are intolerant of MTX at doses ≥ 15 mg per week) before the first dose of study drug. For subjects in Japan, Korea, or Taiwan a stable dose of MTX ≥ 7.5 mg per week is acceptable.
- 22. Subject must have discontinued oral glucocorticoids **or** be on a stable dose of oral glucocorticoid (≤ 7.5 mg per day of prednisone equivalent) for 4 weeks before the first dose of study drug.
- 23. Subjects on oral glucocorticoids (≤ 7.5 mg per day of prednisone equivalent at Baseline) must be willing and able to taper oral glucocorticoids to 0 mg within 4 weeks after the first dose of study drug.
- 24. Subject must have **discontinued all prior b/tsDMARDs and all conventional synthetic (cs)DMARDs, except MTX** prior to the first dose of study drug. The washout periods required prior to the Baseline Visit are specified below or at least 5 times the mean terminal elimination half-life of a drug:
  - ≥ 4 weeks for hydroxychloroquine, cyclosporine, minocycline, penicillamine, sulfasalazine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, bucillamine,

iguratimod, azathioprine, mycophenolate, tocilizumab, sirukumab, sarilumab, and JAK inhibitors (upadacitinib, tofacitinib, baricitinib, filgotinib, ruxolitinib, peficitinib).

- ≥ 4 weeks for etanercept.
- ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, and abatacept.
- ≥ 1 year for rituximab OR ≥ 6 months if B cells returned to pre-treatment level or are in the normal reference range at Baseline, if pre-treatment levels are not available.
- ≥ 8 weeks for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine or activated charcoal as per local label).

25. Subject must not have been treated with any intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath glucocorticoid in the preceding 8 weeks prior to the first dose of the study drug and must not have been treated with super high potency and/or high potency topical glucocorticoids in the preceding 1 week prior to the first dose of study drug.
26. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study or was previously enrolled in this study.
27. Subject must not have received **any live vaccine** within 4 weeks (or longer if required locally) prior to the first dose of study drug or have expected need of live vaccination during study participation including at least 70 days after the last dose of study drug.
28. Subject must have discontinued all opioid and analgesic medications, with the exception of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, combination of acetaminophen with codeine, or combination of acetaminophen with hydrocodone. Subjects entering on analgesics must be on stable dose ≥1 week prior to the first dose of study drug.
29. Subjects must not have been treated with oral traditional Chinese medicine within 4 weeks 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:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy

- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

2. Postmenopausal female
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level ≥ 30 IU/L.

- Females, of Childbearing Potential
    - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 70 days (150 days for UK only) after the last dose of study drug.
    - Females must commit to one of the following methods of birth control:
        - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to Baseline (Day 1).
        - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Baseline (Day 1).
        - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
        - intrauterine device.
        - intrauterine hormone-releasing system.
        - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
        - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

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

During the course of the study, female subjects may change from "of Childbearing Potential" to "of Non-Childbearing Potential" if meeting criteria outlined above under "Females, Non-Childbearing Potential." If needed to confirm post-menopausal status after the screening visit, follicle-stimulating hormone level may be obtained at any time during the study.

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree to use condoms, even if the male subject has undergone a successful vasectomy, from Baseline (Day 1) through at least 70 days (150 days for UK only) after the last dose of study drug.

5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, prior exposure to ABBV-154 or ABBV-3373 are NOT allowed. The following medications are prohibited through the end of study drug administration:

- All csDMARDs, except MTX;
- All tsDMARDs: Examples include but are not limited to the following: Xeljanz® (tofacitinib), Olumiant® (baricitinib), Rinvoq® (upadacitinib), Jyseleca® (filgotinib);
- All bDMARDs, including bio-originators and biosimilars. Examples include but are not limited to the following: Humira® (adalimumab), Enbrel® (etanercept), Remicade® (infliximab), Kineret® (anakinra), Rituxan® (rituximab), Cimzia® (certolizumab pegol), Simponi® (golimumab), Actemra® (tocilizumab), Raptiva® (efalizumab), Tysabri® (natalizumab), Stelara® (ustekinumab), Benlysta® (belimumab), Orencia® (abatacept);
- Through Week 24, oral glucocorticoids with the exception of prednisone ≤ 7.5 mg/d (or equivalent) at Baseline, which must be tapered to 0 within 4 weeks of Baseline unless a subject qualifies for rescue therapy as defined in Section 5.4;
- Any intra-articular, intramuscular, parenteral, trigger point or tender point, intra-bursa, or intra-tendon sheath glucocorticoid through Week 24 unless a subject qualified for rescue therapy defined in Section 5.4;
- Super high potency and high potency topical glucocorticoids;
- Any investigational drugs;
- Any live vaccination;
- Any opioid medications with exception of tramadol, combination of acetaminophen with codeine, or combination of acetaminophen with hydrocodone; and
- Any oral traditional Chinese medicine (e.g., tripterygium glycosides, sinomenine, total glucosides of white paeony).

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded on the appropriate electronic case report form (eCRF) from 30 days prior to Baseline through the Post-Treatment Visit (70 day follow-up). Also, medications taken for RA since the date of diagnosis and any glucocorticoids (based on subject recollection and/or available medical records)

should be entered into the appropriate eCRF inclusive of the first and last dose, dosage, route of administration and reason for discontinuation, if known.

Subjects must remain on stable dose of MTX until Week 24 unless qualifying for rescue therapy as described below. A dietary supplement of oral folic acid (or equivalent, such as folinic acid) should be taken while the subject is taking MTX.

Through Week 24, NSAIDs and low potency analgesics (i.e., acetaminophen, tramadol, combination of acetaminophen with codeine, or combination of acetaminophen with hydrocodone) should continue to be used for the same reason and same dose each time but should not be taken within 24 hours prior to any study visit to avoid bias in outcome measurements.

At Week 18, rescue therapy should be offered to subjects classified as non-responders (defined as not achieving at least 20% improvement in either TJC or SJC at both Week 14 and Week 18) or after Week 18 for at least 2 consecutive visits as follows: 1) add or modify doses of MTX within the range of 7.5-25 mg/week, NSAIDs, acetaminophen/paracetamol, low potency opioid medications (tramadol or combination of acetaminophen and codeine or hydrocodone), oral glucocorticoids (up to maximum dose of prednisone 10 mg/day [or equivalent]) and/or 2) receive 1 intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath glucocorticoids injection every 12 weeks.

At Week 30 and later, subjects classified as non-responders (defined as not achieving at least 20% improvement in either TJC or SJC at both Week 24 and Week 30, or after Week 30 for at least 2 consecutive visits) will discontinue study drug and initiate standard of care therapy at the investigator discretion (e.g., csDMARDs, b/tsDMARDs).

Methotrexate and oral glucocorticoids should be obtained locally as they will not be provided by AbbVie.

Subjects must be able to safely discontinue any prohibited medications as specified in Section 5.1. Subjects must consent to the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility. Information regarding potential drug interactions with ABBV-154 can be located in the ABBV-154 Investigator's Brochure.

Vaccines

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (as per local label) at least 28 days (or longer, if required locally) before first dose of study drug. Live vaccinations are prohibited during study participation including at least 70 days after the last dose of study drug. Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Zostavax (herpes zoster, live attenuated);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles-mumps-rubella-varicella;

- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin;
- Typhoid (oral).

If the live herpes zoster vaccine is to be administered and there is no known history of primary varicella (chicken pox), preexisting immunity to varicella should be confirmed with antibody testing at or prior to Screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative, the live herpes zoster vaccine should not be administered.

Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid or biosynthetic include, but are not limited to, injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted), and pertussis (Tdap) vaccines.

COVID-19 Pandemic -Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of ABBV-154 on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

The first dose of study drug(s) ABBV-154, when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

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

Prednisone or glucocorticoid equivalent of up to 7.5 mg/day is allowed at Baseline. Subjects taking glucocorticoids at Baseline are required to taper the dose to 0 within 4 weeks after the first dose of study drug. A suggested glucocorticoid scheme for the tapering is outlined in Table 1. Adjustment to the suggested glucocorticoid tapering schedule is permitted based on the local availability of

glucocorticoid dosage strengths and individual needs. Signs and symptoms of adrenal insufficiency should be closely monitored (Section 6.2).

Table 1. Suggested Tapering Scheme for Glucocorticoid at Baseline

Study Week	Glucocorticoid Dose at Baseline Per Day					
Baseline	**7 – 7.5 mg**	**6 mg**	**5 mg**	**4 mg**	**3 mg**	**2 mg**
Week 1	5 mg	4 mg	3 mg	3 mg	2 mg	1 mg
Week 2	3 mg	3 mg	2 mg	2 mg	1 mg	1 mg
Week 3	2 mg	2 mg	1 mg	1 mg	0	0
Week 4	1 mg	1 mg	1 mg	0	0	0
Week 5 and beyond	0	0	0	0	0	0

Note: At Week 5, subjects are required to have fully tapered from glucocorticoids.

5.5 Withdrawal of Subjects and Discontinuation of Study

AbbVie may terminate this study prematurely at any time, either in its entirety or partially (discontinue one or more treatment groups), or at any site. The study may be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, data derived from other clinical trials or toxicological studies which negatively influence the benefit-risk assessment might cause discontinuation or termination of the study. 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. Advance notice is not required by either party if the study is stopped due to safety concerns.

A subject may voluntarily withdraw from the study at any time for any reason. An investigator may discontinue a subject's participation at any time for any reason. The AbbVie Therapeutic Medical Director may mandate individual subject discontinuation from study drug in case of a safety concern.

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

- Abnormal laboratory result or AE that meets the criteria for discontinuation of study drug as stated in Section 6.2, or rule out safe continuation of the study drug as determined by the investigator or the AbbVie Therapeutic Area Medical Director.
- Serious infections (e.g., sepsis) that cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk with continuation of the study drug.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- The subject develops anaphylactic reactions or anaphylactic shock.
- The investigator believes it is in the best interest of the subject.

- The subject requests withdrawal from study drug or the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial as determined by the Investigator or AbbVie Therapeutic Medical Director.

State of Emergency or Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix G.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Treatment Group Changes

Treatment group changes at Week 12 (e.g., the re-randomization of subject on placebo) will be done by interactive response technology (IRT) to ensure double-blind integrity.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Discontinuation of Study Drug and Continuation of Study Participation

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should be encouraged to continue to be followed for all regularly scheduled visits as outlined in the Appendix E, and adhere to all study procedures except for administration of study drug, annual TB testing, and PK sample collection, unless a subject decides to discontinue study participation entirely (withdrawal of informed consent). Subjects should continue to be advised on the scientific importance of their data even if they discontinue treatment with study drug early. Following the 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.

In addition, a 30-Day Follow-up Phone Call and a 70-Day Follow-up Visit after the last dose of study drug is required to ensure all treatment-emergent AEs/SAE 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. This information will be recorded on the appropriate eCRF page. This Follow-up Phone Call is not applicable for subjects who discontinue study drug prematurely and continue study participation with completion of at least 1 study visit at least 30 days after the last dose

of study drug. This Follow-up Visit is not applicable for subjects who discontinue study drug prematurely and continue study participation with completion of at least 1 study visit at least 70 days after the last dose of study drug.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy.

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.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

5.7 Study Drug

ABBV-154 or placebo only will be manufactured and provided by AbbVie. It will be taken as SC injections in the abdomen or thigh beginning on Day 1 (Baseline). The study drug (ABBV-154 or placebo) will always be administered by a healthcare/ trained professional up to Week 78 (end of LTE Period 1). For LTE Period 2, study drug will be administered to all subjects by either site medical staff on-site or by the subject or designee (friend, family member, or personal health care professional), if opted for home dosing and where locally permitted. It should be taken at approximately the same time eow, preferably between 7 am and 11 am. A 15- to 30-minute post administration observation time is required. The study drug can be taken with or without food.

ABBV-154 and placebo syringes will be packaged in cartons with quantities sufficient to accommodate the study design. Each prefilled syringe and carton will be labeled per local requirements and these labels must remain affixed to the syringe and carton. Upon receipt, study drug should be stored as specified on the label (refrigerated at 2 to 8 degrees Celsius) 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. Study drug must not be dispensed without contacting the IRT system. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug is for investigational use only and will only be used for the conduct of this study.

AbbVie will provide instructions for drug preparation.

Table 2. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
ABBV-154	Solution for injection/infusion in pre-filled syringe	40 mg and 150 mg	subcutaneous	AbbVie
Placebo for ABBV-154	Solution for injection/infusion in pre-filled syringe	Not applicable	subcutaneous	AbbVie

5.8 Randomization/Drug Assignment

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

At Baseline, 425 subjects will be randomized to 5 treatment groups in a 1:1:1:1:1 ratio to receive ABBV-154: 40 mg, 150 mg, 340 mg SC eow; 340 mg SC e4w, or placebo. Randomization will be stratified by Baseline glucocorticoid (yes/no); number of prior failed b/tsDMARDs (1; 2 or more); and prior anti-TNF failure (yes/no) and if yes further stratification by prior adalimumab use (yes/no). At Week 12, subjects assigned to placebo will be re-randomized in a 1:1 ratio to receive ABBV-154 150 mg or 340 mg SC eow; subjects from the other dose groups will continue with their respective dose and dosing regimen. Re-randomization will be stratified by baseline glucocorticoid use (yes/no) and prior adalimumab use (yes/no). The enrollment for subjects with prior adalimumab use is capped at approximately 30% of the total subjects enrolled.

All AbbVie personnel with direct oversight of the conduct and management of the trial (except for AbbVie Drug Supply Management Team) will be blinded to each subject's treatment through Week 12. The study site personnel and the subject will remain blinded throughout the study. To maintain the blind, the ABBV-154 and placebo pre-filled syringes provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring and Glucocorticoid Adjudication Committees

An external DMC will be established to safeguard the interest of trial subjects by assessing the safety of the interventions during the trial and well as for the monitoring the integrity and interpretability of the trial. 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 expectations for blinded communications.

An independent glucocorticoid adjudication committee will be established to adjudicate systemic glucocorticoid AEs. A separate charter will be prepared, outside of the protocol, and will describe the roles and responsibilities of the adjudication committee members, frequency of data reviews, and expectations for blinded communications.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

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

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

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/or 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 events are reported, then the following supplemental report must be completed.

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 eCRF
Renal impairment **Renal dysfunction** **Renal failure** **Serum creatinine >1.5 x the Baseline value and >ULN**	Renal eCRF
Adrenal insufficiency	Adrenal insufficiency eCRF
COVID-19 infection	COVID-19 eCRF

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; eCRF = electronic case report form; COVID-19 = coronavirus pandemic 2019; MACE = major adverse cardiac event; SAE = serious adverse event; ULN = upper limit of normal

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual [Appendix G] for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an investigation medicinal product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria.

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

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

Safety Topics of Interest

The following safety topics of interest will be monitored during the study:

- Serious infections;
- Opportunistic infections;
- Active TB;
- Serious allergic reactions;
- Hypersensitivity reactions;
- Malignancies;
- Systemic glucocorticoid side effects;
- Adrenal insufficiency; and
- Iatrogenic Cushing's Syndrome.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0).[3]

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 24 hours of site awareness of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 70 days following the last dose of study drug.

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

6.2 Toxicity Management

The management of specific AEs and laboratory parameters are presented in Table 3. 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 laboratory) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Elective surgery will not be allowed during the first 24-weeks of study participation. If the subject undergoes elective surgery, study drug should be interrupted at least 2 weeks prior to the planned surgery. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Management of Hypersensitivity and Serious Allergic Reactions

Subjects should be closely monitored and assessed for the development of signs and symptoms of hypersensitivity reactions, including anaphylaxis. For any hypersensitivity reaction, appropriate therapy should be instituted per standard of care. Study drug should be discontinued if a subject develops anaphylaxis.

In the event of a suspected systemic post-dose hypersensitivity reaction, if the clinical situation allows, every effort should be made to obtain a serum sample within 2 hours but no later than 6 hours from

symptom onset for additional blood tests specified in the Operations Manual, Section 3.15 Hypersensitivity Testing.

Management of Serious Infections

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

Management of Malignancy

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

Management of Demyelinating Disease

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

Management of Hypertension

Subjects should be closely monitored for the development of hypertension. Investigators should consider stopping the study drug if hypertension is not successfully controlled under standard of care.

Management of Hyperglycemia

Subjects should be closely monitored for the development of hyperglycemia. Investigators should manage the hyperglycemia with appropriate standard of care.

Management of Glucocorticoid Induced Adrenal Insufficiency

Subjects should be closely monitored for signs and symptoms of adrenal insufficiency (e.g., nausea, vomiting, lightheadedness, pale skin, unexplained weight loss, low blood pressure, electrolyte abnormalities [e.g., confirmed hyponatremia < 135 mmol/L, hyperkalemia > 5.5 mmol/L], etc.) and if adrenal insufficiency is suspected, further clinical assessment and management should follow local standard of care and may include measuring of cortisol levels and/or ACTH stimulation test to be performed at a local laboratory. Glucocorticoid therapy with physiologic doses should be considered. After withdrawal of glucocorticoid therapy, adrenal insufficiency may persist for months; therefore, glucocorticoid therapy should be considered in any situation of stress (e.g., serious infection) occurring or in the months following withdrawal of study drug.

Management of COVID-19

Subjects should be closely monitored for COVID-19. Study drug should be interrupted if a subject develops a confirmed diagnosis of COVID-19. Consider the interruption of study drug in subjects with signs and/or symptoms and suspicion of COVID-19.

Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for selected abnormal laboratory values are described in Table 3, and may require a supplemental eCRF to be completed (Section 6.1). For subjects with ongoing laboratory abnormalities that require data entry into an eCRF, an additional eCRF related to subsequent laboratory abnormalities is only required if the subject has relevant changes in history (e.g., new onset signs or symptoms) or laboratory values that have returned to normal reference range or its Baseline value followed by subsequent laboratory abnormalities meeting toxicity guidelines (considered a new event). 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 the Operations Manual (Appendix G) Section 3.15, the repeat testing must occur as soon as possible.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Absolute neutrophil count	If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its BL value. Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
Absolute lymphocyte counts	If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its BL value.
Platelet count	If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its BL value.
AST or ALT	Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5. A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from Baseline). • Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD. Subjects with HBc Ab+ (irrespective of HBs Ab status) or Hbs Ab+ (without a history of vaccination) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA PCR testing performed within one week (based on initial elevated value): • ALT> 5 × ULN OR • ALT or AST > 3 × ULN if an alternative cause is not readily identified. • Note: A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST. A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment. 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. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	If serum creatinine is > 1.5 × the BL value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × BL value and ≤ ULN. For the above serum creatinine elevation scenario, complete the appropriate supplemental renal eCRF(s).

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

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The primary analysis will be conducted after all ongoing subjects have completed Week 12. This will be the only and final analysis for the Double-Blind, Placebo-Controlled Period. After the primary analysis, additional analyses may be conducted to further inform the design of a Phase 3 program. A final analysis will be conducted after all subjects have either withdrawn from the study or completed LTE Period 2 plus the safety follow-up visit. To maintain integrity of the trial, the study sites and subjects will remain blinded until all subjects have either completed the last visit of LTE Period 1 or have withdrawn from the study.

7.2 Definition for Analysis Populations

The following populations will be used for analyses:

- Intent-to-treat Population includes all subjects who were randomized and received at least 1 dose of study drug. The ITT Population will be used for all efficacy analyses.
- Safety Population in the Placebo-Controlled Period (Safety_PC) includes all subjects randomized and received at least 1 dose of study drug. This population will be used for the safety analysis in the Placebo-Controlled Period.
- All ABBV-154 Treated Population (ALL_154) includes all subjects who received at least 1 dose of ABBV-154 during the study. This population will be used to provide a comprehensive summary of safety.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

No intercurrent events will be considered for the primary and secondary endpoints.

7.4 Statistical Analyses for Efficacy

For the Placebo-Controlled Period, subjects will be analyzed according to the treatment group randomized. All statistical tests will be performed at a 2-sided significance level of 0.1. A 95% confidence interval of the treatment difference between each ABBV-154 dose and placebo will be provided.

- For categorical variables, a pairwise, comparison will be made between each ABBV-154 dose and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the actual values of stratification factors. Non-Responder Imputation incorporating multiple imputation to handle COVID-19 (NRI-MI) will be the primary approach to handle missing data for categorical endpoints.
- For continuous variables, the comparison will be made between each ABBV-154 dose and placebo based on the MMRM adjusting for treatment, visit, interaction between treatment and visit, actual values of stratification factors as fixed factors, and BL value as a covariate. The MMRM will be the primary approach to handle missing values for continuous endpoints.

Through the Placebo-Controlled and Long-Term Extension Periods, descriptive statistics by treatment sequences will be provided at each visit. Categorical endpoints will be summarized by the number and proportion of subjects who achieved the endpoint, as well as the 95% confidence interval. Continuous endpoints will be summarized by descriptive statistics including mean, standard deviation, standard error, and the 95% confidence interval of the mean. In addition, continuous endpoints through Week 24 will be summarized using estimates from the MMRM by treatment sequence, visit, interaction between treatment sequence and visit, actual values of stratification as fixed factors and baseline values as a covariate.

Summary and Analysis of the Primary Endpoint

The primary endpoint is the achievement of ACR50 at Week 12. It will be evaluated using the ITT Population based on treatment as randomized. Comparison of the primary endpoint will be made between each ABBV-154 dose and placebo using the CMH test adjusting for the actual values of stratification factors. NRI-MI will be the primary approach to handle missing values. Analysis details for NRI-MI and other sensitivity analyses (if applicable) will be provided in the SAP.

One supplementary analysis for primary endpoints is to test a pre-specified set of dose-response models among ABBV-154 dose groups and the placebo group at Week 12 using the Multiple Comparison Procedure – Modeling approach (MCP-Mod). Details of this method will be provided in the SAP.

Summary and Analysis of Secondary Endpoints

Analysis of secondary efficacy endpoints will be conducted on the ITT Population based on treatment as randomized.

Summary and Analysis of Additional Efficacy Endpoints

Additional endpoints, as described in Section 3.3, will also be analyzed.

Subgroup Analysis for Efficacy

To evaluate the consistency of efficacy across demographic and other Baseline characteristics, the following subgroup analysis will be performed on the primary endpoint:

- Baseline glucocorticoid use (yes/no)
- Number of prior failed b/tsDMARDs (1; 2 or more)
- Prior use of failed anti-TNF (yes/no)
- Prior use of adalimumab (yes/no)
- Age (≤ median/>median)
- Sex (female/male)
- Race (white/non-white)

7.5 Statistical Analyses for Safety

All safety analyses will be performed based on the Safety Population, as defined in Section 7.1. Subjects will be analyzed based on the actual treatment received. Treatment-emergent adverse events (TEAEs), laboratory assessments, and vital signs will be summarized. Key safety variables will also be summarized on the ALL_154 Population.

A TEAE for the Safety Population is defined as an AE newly occurred or worsened after the first dose of study drug and within 70 days after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA system organ class and Preferred Term, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient years) of SAEs, deaths, and AEs leading to discontinuation will be provided as well. Pre-treatment AEs will be summarized separately.

For selected laboratory parameters, a listing of all subjects with any laboratory value ≥ Grade 3 of the Common Toxicity Criteria will be provided. Mean change in laboratory and vital signs variables will be summarized. Additional details for the safety analysis are provided in the SAP.

7.6 Statistical Analysis for Pharmacokinetics and Immunogenecity

Concentrations of conjugated ADC, total antibody, and free payload (A-1677770) will be summarized at each time point using descriptive statistics.

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

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

7.7 Statistical Analysis of Biomarker Data

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

7.8 Interim Analysis

Interim analyses may be performed in this study.

7.9 Overall Type 1 Error Control

Multiplicity from multiple comparisons is not adjusted in this Phase 2b study.

7.10 Sample Size Determination

The planned total sample size of 425 subjects (approximately 85 subjects per treatment group) provides at least 90% power to detect a 22% difference between ABBV-154 and placebo in ACR50 response rate at Week 12 (assuming a placebo ACR50 response rate of 13%), at 2-sided significance level of 0.1 based on Chi-square test.

8 Ethics

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

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

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study

conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix C.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subject against an immediate hazard.

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).

In case of state of emergency or pandemic situations (e.g., During the COVID-19 pandemic), remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study sites.

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

The end-of-study is defined as 70 days after the last study drug administration.

12 REFERENCES

1. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther. 2002;96(1):23-43.

2. AbbVie. ABBV-154 Investigator Brochure Edition 2. 2020.

3. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 2017 [cited 2019 October 16]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

4. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
ACR 20/50/70	ACR 20/50/70
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BMD	bone mineral density
BMI	body mass index
BSAP	Bone specific alkaline phosphatase
b/tsDMARD	biologic and targeted synthetic disease-modifying antirheumatic drugs
CDAI	clinical disease activity index
CMH	Cochran-Mantel-Haenszel
COVID-19	COVID-19
CR	clinical remission
CRF	case report form
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTX	C-terminal telopeptide of type 1 collagen
CXR	chest x-ray
DAS28	disease activity score (28 joints)
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DXA	dual-energy X-ray absorptimometry
e4w	every 4 weeks
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

eow	every other week
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FSH	follicle stimulating hormone
GCP	good clinical practice
GRMs	glucocorticoid receptor modulators
HAQ-DI	Health Assessment Questionnaire Disability Index
HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBsAg	hepatis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	HCV antibody
HIV	human immunodeficiency virus
HPA	hypothalamic pituitary-adrenal axis suppression
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IU	International units
LCMS	liquid chromatography-mass spectrometer
LDA	low disease activity
LTE	long term extension
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Model Repeated Measurements
MTX	methotrexate
nAb	neutralizing antibody
NMSC	non-melanoma skin cancer
NRI-MI	non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19
NRS	numerical rating scale

NSAID	non-steroidal anti-inflammatory drug
OC	osteocalcin
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PFS	pre-filled syringes
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PPD	purified protein derivative
RA	rheumatoid arthritis
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SDAI	simplified disease activity index
SF	short form
SJC	swollen joint count
SUSAR	suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TBNK	T/B and natural killer cells
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
ULN	upper limit of normal
vs.	versus

APPENDIX B. 2010 RHEMATOID ARTHRITIS CLASSIFICATION

The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis[4]

Target population (Who should be tested?): Patients who: 1) have at least 1 joint with definite clinical synovitis (swelling)[a] and 2) with the synovitis not better explained by another disease[b]

A score of ≥ 6/10 is required for classification of a patient as having definite RA.[c]

Classification Criteria for Rheumatoid Arthritis (Add scores in each category)	Score
Joint involvement[d]	
1 large joint	0
2-10 large joints 1	1
1-3 small joints (with or without involvement of large joints)[e]	2
4-10 small joints (with or without involvement of large joints)	3
> than 10 joints (at least 1 small joint)[f]	5
Serology (at least 1 test result is needed for classification)[g]	
Negative rheumatoid factor and negative anti-citrullinated protein antibody ACPA	0
Low-positive rheumatoid factor or low-positive anti-citrullinated protein antibody	2
High-positive rheumatoid factor or high positive anti-citrullinated protein antibody	3
Acute-Phase Reactants (at least 1 test result is needed for classification)[h]	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of Symptoms[i]	
< 6 Weeks	0
≥ 6 Weeks	1

CRP = C-reactive protein; ESR = erythrocyte sedimentation Rate

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

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

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

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

e. "Large joints" refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

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

g. Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor information is only available as positive or negative, a positive result should be scored as low-positive for rheumatoid factor.

h. Normal/abnormal is determined by local laboratory standards.

i. Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

APPENDIX C. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-466: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to Biologic and/or Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs (b/tsDMARDs)

Protocol Date: 12 April 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 D. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Senior Medical Writer	Medical Writing
[redacted]	Group Medical Director	Immunology Therapeutic Area
[redacted]	Medical Director	Immunology Therapeutic Area
[redacted]	Associate Director	Statistics
[redacted]	Therapeutic Area Head	Statistics
[redacted]	Director	Clinical Pharmacology

APPENDIX E. ACTIVITY SCHEDULE

The following table shows the required activities across all subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications in case of emergency or pandemic situations due to COVID-19 are detailed in the Operations Manual.

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
INTERVIEWS & QUESTIONNAIRES																								
Subject information and informed consent	✓																							
Eligibility criteria	✓	✓																						
Medical/surgical history	✓	✓																						
Alcohol and nicotine use	✓																							
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB risk assessment questionnaire	✓																Wk 54			Wk 110, 166				
Patient's Assessment of Pain		✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓		
Patient's Assessment of Disease Activity		✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓		

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
HAQ-DI		✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓		
PROMIS® Pain Interference (8-item short form)		✓			✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		
FLARE – RA		✓			✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		
PGIS – FLARE		✓			✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		
PGIC – FLARE									✓						✓			✓				✓		
LOCAL LABS & EXAMS																								
Body Weight	✓	✓	✓	✓	✓				✓	✓		✓			✓		✓	✓	✓	✓	✓	✓		✓
Height	✓																							
Vital Signs	✓	✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓		✓
Physical Exam	✓	✓							✓						✓		Wk 36, 48, 60, 72	✓	✓	Wk 94, 118, 142, 166	✓	✓		

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
12-lead ECG	✓								✓						✓		Wk 36	✓		Wk 134	✓	✓		
Chest x-ray	✓																Wk 54 if applicable			Wk 110 and 166 if applicable					
DXA (Bone Density, Body Composition) Scan	✓														✓			✓		Wk 134	✓				
Physician's Global Assessment of Disease Activity		✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓			
TJC68 and SJC66	✓	✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓			
Erythrocyte sedimentation rate	✓																							

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
Urine pregnancy test (for female of childbearing potential)		✓			✓		✓		✓		✓		✓		✓	Wk 28, 32, 40, 44, 52, 56, 64, 68, 76	Wk 36, 48, 60, 72	Wk 78, 82	✓	Wk 90, 94, 98, 102, 106, 110, 114, 118, 122, 126, 130, 134, 138, 142, 146, 150, 154, 158, 162, 166, 170, 174, 178		✓			✓
CENTRAL LABS																								
Serum pregnancy test (females of child-bearing potential): FSH, if applicable	✓																							
hsCRP	✓	✓	✓	✓	✓		✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓		
TSH	✓																							
Anti-citrullinated protein antibody	✓																							

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
Rheumatoid Factor	✓														✓			✓			✓			
Hematology	✓	✓		✓	✓		✓		✓	✓		✓			✓		✓	✓	✓	✓	✓	✓		✓
HbA1c	✓	✓							✓						✓		Wk 36, 48, 60, 72			Wk 94, 118, 142, 166	✓			✓
Clinical chemistry and urinalysis	✓	✓		✓	✓		✓		✓	✓		✓			✓		✓	✓	✓	✓	✓	✓		Clinical chemistry only
Lipid profile		✓							✓						✓		Wk 36, 48, 60, 72			Wk 94, 118, 142, 166	✓			
TB Test (QuantiFERON TB Gold test and/or local lab purified protein derivative skin test)	✓																Only Wk 54			Wk 110 and 166				
HIV, HBV, and HCV Note: HBV test every 12 weeks only if required due to local regulations.	✓								✓						✓		E12W if applicable							

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
Blood samples for conjugated ADC (serum), total antibody (serum), free A-1677770 (plasma) assays		✓	✓	✓	✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		✓
Blood samples for serum ADA assays (including ADA titer and nAb, assays)		✓			✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		✓
Blood sample for total cortisol		✓	✓	✓	✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		✓
Biomarker sample whole blood for bone marker P1NP, OC, CTX, and BSAP		✓	✓	✓	✓		✓		✓			✓			✓		✓	✓						
Biomarker sample whole blood for free cortisol		✓	✓	✓	✓		✓		✓			✓			✓		✓	✓	✓	✓	✓	✓		✓
Biomarker sample whole blood for ACTH		✓			✓		✓		✓			✓			✓		✓	✓						
Biomarker sample whole blood for TBNK		✓	✓	✓			✓		✓			✓			✓		✓	✓						

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
Optional biomarker samples: plasma/serum proteomic		✓	✓	✓			✓		✓			✓			✓									
Optional biomarker samples: PBMC		✓	✓	✓			✓		✓			✓			✓									
Optional biomarker: samples: whole blood RNA		✓	✓	✓			✓		✓			✓			✓									
Optional biomarker: samples: whole blood DNA		✓	✓	✓			✓		✓			✓			✓									
℞ TREATMENT																								
Randomization/ drug assignment		✓							✓															
Supervised training for study drug administration at home																Wk 76		✓						
Dispensation of study drug for home administration																		✓	✓	✓				

Activity	Screening	Baseline	D 4	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Double-Blind LTE Period 1			LTE Period 2			PD Visit	30-D F/U Phone Call	70-D F/U Visit
																EOW Visits	E6W Visits	Wk 78	Wk 86	E8W Visits	Wk 182			
	Day –35 to Day -1	Day 1	Day 4	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E6W Visits	Day 547	Day 603	E8W Visits	Day 1,275			
Subject dosing diary review																			✓	✓	✓			
Administration study drug until Week 180		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				

Ab = antibody; ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; ADC = antibody-drug conjugate; D = day; DNA = deoxyribonucleic acid; DXA = dual-energy X-ray absorptimometry; ECG = electrocardiogram; EOW = every other week; E6/8/12W = every 6/8/12 weeks; FSH = follicle stimulating hormone; F/U = follow-up; HAQ-DI = Health Assessment Questionnaire Disability Index; HBV = hepatitis b virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; LTE = long-term extension; nAb = neutralizing antibody; PBMC = peripheral blood mononuclear cell; PD = premature discontinuation; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; RA = rheumatoid arthritis; SJC = swollen joint count; TB = tuberculosis; TBNK = T/B and natural killer cells; TJC = tender joint count; TSH = thyroid stimulating hormone; WK = week

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	23 April 2021
Version 1.1 (Japan Only)	10 May 2021
Administrative Change 1	06 July 2021
Version 1.2 (United Kingdom Only)	17 September 2021

The purpose of this version is to update the following sections below. In addition, minor typographical corrections or edits have been made for consistency throughout the Protocol and Operations Manual.

Summary of Protocol Changes:

- Protocol Section 1, Synopsis; Protocol Section 4.1, Overall Study Design and Plan: Added a 104-week LTE Period 2 and renamed the originally planned double-blind LTE period "Double-Blind, Long-term Extension Period 1." Corrected spelling of glucocorticoid.

  Rationale: *The 2 LTEs are labeled "Double-Blind, Long-term Extension Period 1" and "Long-term Extension Period 2" to differentiate between them as the first LTE period is double-blind and the second LTE period will be blinded only until the last subject completes the last visit of Double-Blind Long-term Extension Period 1 or withdraws from the study. The 104-week LTE Period 2 will collect additional data for the long-term safety, tolerability, and efficacy of ABBV-154 in subjects with RA who have completed Double-Blind LTE Period 1.*

- Protocol Section 1, Synopsis, Investigational Plan: Follow-up "Visit" changed to Follow-up "Period."

  Rationale: *To reflect the duration of follow-up, as the follow-up period is now comprised of a follow-up phone call and a follow-up visit as opposed to a single visit.*

- Protocol Section 1, Synopsis; Protocol Section 4.1, Overall Study Design and Plan; Protocol Section 7.1, Statistical and Analytical Plans: Updated wording to indicate that blinded dosing regimens will be continued until all subjects having either completed the last visit of LTE Period 1 or have withdrawn from the study.

  Rationale: *To specify when unblinding will occur.*

- Protocol Section 1, Synopsis; Protocol Section 5.1, Eligibility Criteria: Updated criterion #7 to include a list of b/tsDMARDs that can be considered for the criteria of inadequate response, including guidance for previous use of investigational drugs. Updated note on the criterion #7 to clarify that b/tsDMARDs discontinued due to other reasons unrelated to inadequate response will not be accepted to fulfill eligibility criteria.

  Rationale: *To clarify which b/tsDMARDs are acceptable to fulfil the criterion #7 by mechanism of action, including guidance for previous use of investigational drugs. To clarify that b/tsDMARDs*

discontinued due to other reasons unrelated to inadequate response will not be accepted to fulfill eligibility criterion #7.

- Protocol Section 3.1, Objectives, Hypotheses, and Estimands; Protocol Section 7.2, Definition of Analysis Populations: Changed the definition of ITT population from all randomized subjects to all subjects who were randomized and received at least 1 dose of study drug.

  Rationale: *To exclude subjects from the ITT analysis if they were not dosed to be consistent with analysis methods used in prior clinical trials, which included all randomized subjects who received at least 1 dose of study drug.*

- Protocol Section 3.1, Objectives, Hypotheses, and Estimands; Protocol Section 7.3, Handling Potential Intercurrent Events for the Primary and Secondary Endpoints: Removed the intercurrent event of confounding medication use for all endpoints.

  Rationale: *Medications with potential to affect efficacy are either prohibited through the placebo-controlled period or are required to remain at stable dose (as listed in Protocol Section 5.1, Eligibility Criteria, and Protocol Section 5.3, Prohibited Medications and Therapy). Handling of intercurrent events of confounding medication use was removed to allow comparison to prior clinical trials that did not use this analysis method, as this study will be used to inform future development of ABBV-154.*

- Protocol Section 3.7 Biomarker Research Endpoints; Appendix E, Activity Schedule; Operations Manual Section 2.1, Individual Treatment Period Visit Activities; Section 3.9 Biomarker Research Sampling; Section 4.1 Methods and Timing of Safety Assessment; Appendix 7.3, Synovial Biopsy Procedures: Removed mention of synovial biopsy/joint biopsy.

  Rationale: *The Optional Synovial Biopsy Substudy has been removed as it has been determined it will not be possible to enroll enough subjects into the Substudy to achieve scientific goals; without expectation for the data to provide meaningful scientific value it is not appropriate to perform the biopsy procedure on study subjects.*

- Protocol Section 4.1, Overall Study Design and Plan: Added 70-Day Follow-up Period to the description of the overall study design.

  Rationale: *To provide clarity surrounding the planned duration of the study.*

- Protocol Section 4.1, Overall Study Design and Plan; Protocol Section 7.1, Statistical and Analytical Plans: Updated timing of the Primary Analysis and the Final Analysis to specify it will occur after all ongoing subjects have completed Week 12 or have withdrawn from the study.

  Rationale: *To provide clarification for analysis timing.*

- Protocol Section 4.1 and Figure 1: Updated text and figure to include the 104-week LTE Period 2. Updated text to clarify that subjects previously on placebo will be re-randomized.

  Rationale: *Figure was updated to reflect changes in the study design with the addition of the 104-week LTE Period 2. Updated text regarding re-randomization of placebo subjects for clarity.*

- Protocol Section 5.1, Eligibility Criteria: Updated criterion #3 to add "at the time of Screening."

  Rationale: *To clarify timepoint for which this criterion is to be applied.*

- Protocol Section 5.1, Eligibility Criteria: Updated criterion #4 to correct units to "mIU/L."

  Rationale: *To correct the typographical error.*

- Protocol Section 5.1, Eligibility Criteria, Protocol Section 5.2, Contraception Recommendations: Specified the duration of contraception requirements will be 150 days (5 months) after last dose of study drug administration for females (criterion #15) (UK only) and for males (criterion #17) (UK only). Specified that females must not be pregnant, breastfeeding, or considering becoming pregnant and must not donate eggs for 150 days after last dose of study drug administration (criterion #16) (UK only), and males must not consider fathering a child or donating sperm for 150 days after last dose of study drug administration (criterion #18) (UK only). Updated bullet for Females, Childbearing Potential to add that females of childbearing potential must avoid pregnancy for 150 days (UK only) after the last dose of study drug. Updated Contraception Requirements for Males to add that males who are sexually active with a female partner of childbearing potential must use male condoms through at least 150 days (UK only) after last dose of study drug.

  Rationale: *The duration of contraception, pregnancy, and egg/sperm donation requirements after last dose of study drug was changed for the UK to align with local health authority request. The duration for each remains 70 days after the last dose of study drug administration globally, which represents greater than 5 times the upper limit of the mean elimination half-life, using the most conservative estimate of the half-life among the 3 analytes (ADC, total antibody, and payload) measured in circulation following subcutaneous administration of ABBV-154. Thus, at 70 days, no relevant systemic exposure to ABBV-154 is expected to be present.*

- Protocol Section 5.1, Eligibility Criteria: Updated criterion #24 to add "interventional" to describe clinical study type.

  Rationale: *To specify that subjects cannot be enrolled in another interventional study. Noninterventional studies are permitted, as they are not expected to impact safety or efficacy of this study.*

- Protocol Section 5.1, Eligibility Criteria: For criterion #25, corrected a typographical error in the period of time to refrain from live vaccination after last dose of study drug from 12 weeks to 70 days and add clarification that 4 weeks is the minimum amount of time between receipt of a live vaccine, but duration may be longer if required locally.

  Rationale: *To align with Protocol Section 5.4 and to ensure that a live vaccination is not administered during periods of relevant systemic ABBV-154 exposure, as 70 days is greater than 5 times the upper limit of the mean elimination half-life of subcutaneously administered ABBV-154.*

- Protocol Section 5.2, Contraception Recommendations: Corrected requirement #1 for Females, Non-Childbearing Potential to "Premenopausal" from "Postmenopausal." Corrected the follicle-stimulating hormone level to ≥ 30 IU/L from > 30 IU/L.

  Rationale: *To correct the typographical errors.*

- Protocol Section 5.2, Contraception Recommendations: updated that both male and female condoms may be used where required by local practices in addition to the highly effective methods of birth control.

  Rationale: *To clarify that where required by local practices, both male and female condoms may be used in addition to the highly effective methods of birth control which are required for all*

Females, of Childbearing Potential as either will adequately prevent the occurrence of pregnancy.

- Protocol Section 5.2, Contraception Recommendations: Added language to allow re-testing with follicle-stimulating hormone after screening visit for female subjects that may change status from childbearing potential to non-childbearing potential during the course of the study.

  Rationale: *During the course of the study, females initially classified as of childbearing potential may become postmenopausal or permanently sterile and therefore not at risk to become pregnant. For subjects not at risk for pregnancy, discontinuation of required contraception and pregnancy testing is appropriate.*

- Protocol Section 5.3, Prohibited Medications and Therapy: Changed the time period during which the list of prohibited medications is prohibited from "throughout the duration of the study" to "through the end of study drug administration."

  Rationale: *To clarify that subjects may receive these medications after discontinuation of study drug.*

- Protocol Section 5.3; Prohibited Medications and Therapy: Corrected "sheet" to "sheath."

  Rationale: *To correct the typographical error.*

- Protocol Section 5.4, Prior and Concomitant Therapy: Deleted text describing b/tsDMARDs by mode of action and text stating all csDMARDs except for MTX must have been discontinued.

  Rationale: *As information on prior b/tsDMARD therapies which would qualify a subject for study eligibility was added to eligibility criterion #7 this information was removed from Section 5.4 to avoid duplication of information and potential for confusion. The requirement for discontinuation of all prior b/tsDMARDs and all csDMARDs, except MTX prior to the first dose of study drug was deleted to remove redundancy and potential confusion as it is included in eligibility criterion 22 and Section 5.3, Prohibited Medications and Therapy with requirements for MTX stability remaining in Section 5.4.*

- Protocol Section 5.4, Prior and Concomitant Therapy: Clarified that at Week 30 and later, subjects classified as non-responders (defined as not achieving at least 20% improvement in either TJC or SJC at both Week 24 and Week 30, or after Week 30 for at least 2 consecutive visits) will discontinue study drug and initiate standard of care therapy at the investigator discretion.

  Rationale: *To improve clarity.*

- Protocol Section 5.5, Withdrawal of Subjects and Discontinuation of Study: Updated to state that AbbVie may terminate this study prematurely "at any time," either in its entirety or "partially discontinue one or more treatment groups."

  Rationale: *To clarify that AbbVie may prematurely discontinue not just the entire study but one or more treatment groups at any time.*

- Protocol Section 5.5, Withdrawal of Subjects and Discontinuation of Study: Added the following wording to bullet #1 regarding abnormal laboratory results or AEs that meets the criteria for discontinuation of study drug, "or rule out safe continuation of the study drug" as determined by the investigator.

Rationale: *To clarify that the investigator or AbbVie TA MD may also determine that a subject must be discontinued from study drug based on abnormal laboratory result or AE, which prevents safe continuation of the study drug even if not stated in Section 6.2, Toxicity Management.*

- Protocol Section 5.6, Follow-Up After Subject Discontinuation of Study Drug or From Study, and Operations Manual Section 2.2 Post-Treatment Activities: Added "30-Day Follow-up Phone Call" and to clarify those subjects for whom the Follow-up Phone Call and Follow-up Visit are not applicable.

  Rationale: *Phone call was added to further ensure subject safety and capture of AEs/SAEs occurring early in the follow up period. The follow-up phone call and follow-up visit are not required to collect additional subject data if a subject continues in the study for at least 30 days or 70 days, respectively, as follow-up will occur at regular study visits.*

- Protocol Section 5.7, Study Drug; Operations Manual Section 6.1, Treatment Administered: Removed reference to 3 SC injections (2 PFS with 1.5 ml fill volume and 1 PFS with 0.4 ml fill volume).

  Rationale: *Text on number of injections/syringes with specific volumes was removed to allow dispensing of fewer kits based on assigned treatment once study is unblinded, as placebo injections are no longer required at that time.*

- Protocol Section 5.7, Study Drug: Corrected time range for study drug administration to be between 7 a.m. and 11 a.m. Added sentence explaining that for LTE Period 1, the study drug (ABBV-154 or placebo) will always be administered by a healthcare/ trained professional and for LTE Period 2, study drug will be administered to all subjects by either site medical staff on-site or by the subject or designee (friend, family member, or personal health care professional), if opted for home dosing and where locally permitted.

  Rationale: *To correct the typographical error for consistency with the Operations Manual. To clarify the study drug administration during both LTE Period 1 and LTE Period 2.*

- Protocol Section 6.1, Complaints and Adverse Events: Removed "AE" from the Hepatic eCRF.

  Rationale: *The eCRF is applicable both for specified hepatic-related AEs and laboratory abnormalities.*

- Protocol Section 6.1, Complaints and Adverse Events: Updated wording to state that pregnancy in a study subject must be reported to AbbVie within 24 hours of site awareness.

  Rationale: *To provide clarification.*

- Protocol Section 6.2, Toxicity Management: Added sentence explaining that toxicity management requirements do not apply to a subject who is discontinued from study drug but continues study participation.

  Rationale: *To clarify applicability of toxicity management requirements as no ongoing risk to subject safety related to study drug is anticipated after discontinuation of study drug administration.*

- Protocol Section 6.2, Toxicity Management: Added instructions for interruption of study drug at the time of elective surgery and clarified when to re-start study drug after surgery.

Rationale: *To ensure subject safety by providing instructions for interruption of study drug related to surgery.*

- Protocol Section 6.2, Toxicity Management: Added sentence to Management of Select Laboratory Abnormalities explaining situations in which subjects with ongoing laboratory abnormalities do not require additional data entry into an eCRF.

  Rationale: *To clarify and reduce duplication of eCRF data entry.*

- Protocol Appendix A, Study-Specific Abbreviations and Terms: Updated abbreviations list.

  Rationale: *Added missing abbreviation for PBMC and reordered abbreviations alphabetically where needed.*

- Protocol Appendix D, List of Protocol Signatories: Updated personnel list.

  Rationale: *Administrative change.*

- Protocol Appendix E, Activity Schedule: Updated the Activity Schedule (Appendix E) to reflect changes in the study design and to include additional activities for specific visits. Updated abbreviations list at end of table.

  Rationale: *To reflect all the changes in activities scheduled on specific visits and additional abbreviations.*

- Operations Manual, Section 1 Contacts: Updated the name of the Certified Clinical Lab to Labcorp Central Laboratory and updated the name and contact of the Biomarker Sample storage from Brooks Life Sciences Brooks Receiving to Azenta Life Sciences.

  Rationale: *The name of the certified clinical lab changed from Covance Central Laboratory to Labcorp Central Laboratory and the name of the biomarker sample storage changed to Azenta Life Sciences.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities; Section 2.2 Post-Treatment Activities: Added an extra column/dot to the column headers of the Individual Study Day tables.

  Rationale: *To reflect the addition of the 30-day post-treatment follow-up phone call.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities: Deleted subsequent instances of full terms for high-sensitivity C-reactive protein and Health Assessment Questionnaire Disability Index since already defined at first use and acronym provided.

  Rationale: *To remove redundancy.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities: Added "Rheumatoid Factor" for Week 78 visit.

  Rationale: *Added to align with Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visit Activities: Added a 7-day treatment period window for the LTE Period 2, starting at Week 86.

  Rationale: *To inform that a longer treatment window period of 7 days will be allowed for the LTE Period 2. This will give flexibility to the subjects that opted for dosing at home and will maintain the 7-day treatment window considered safe between doses.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities: Corrected the spelling of "virtual."

  Rationale: *To correct the typographical error.*

- Operations Manual, Section 2.1: Updated study visit day tables and individual visit activities for LTE Period 1, LTE Period 2, 30-Day Follow-Up Phone Call, Week 182 Final Study Visit, and 70-day Follow-up Visit.

  Rationale: *To reflect updated schedule of activities as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities: Corrected the AE assessment during the Screening Period to only study procedure-related SAEs and non-serious AEs.

  Rationale: *To align with the Operations Manual Section 4.1 Methods and Timing of Safety Assessment.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Week 26, 28, 32, 34, 38, 40, 44, 46, 50, 52, 56, 58, 62, 64, 68, 70, 74, 76: Added supervised training for study drug administration at home at Week 76 and corresponding footnote "a" to inform that if administration of study drug at home is not locally permitted or not opted by the subject, training for home administration is not required.

  Rationale*: To ensure proper training for subjects which will be dosing at home during LTE Period 2 and clarify that if administration of study drug at home is not locally permitted or not opted by the subject, training for home administration is not relevant.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities, Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 18 (Day 127), Week 24 (Day 169), Week 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174, Week 182 (Final Study Visit), Premature Discontinuation: Removed definition of ADA (anti-drug antibody) and nAb (neutralizing antibodies) abbreviations.

  Rationale: *Definition of ADA and nAb abbreviations were provided on Week 2 (Day 15).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Added the TB risk questionnaire, QuantiFeron-Tb Gold test (and/or local PPD Skin Test), and Chest X-ray to Weeks 110 and 166.

  Rationale: *To ensure subject safety through annual TB assessments during administration of study drug.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Updated PGIC – FLARE to Week 78 only.

  Rationale: *To align with the activity schedule Appendix E for the LTE Period 1 where PGIC – FLARE is performed at Week 78.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: updated PGIS –

FLARE to Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, and 174.

Rationale: *To reflect the updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Updated the physical exam to Weeks 36, 48, 60, 72, 78, 86, 94, 118, 142, and 166.

  Rationale: *To reflect updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Updated 12-lead ECG to Weeks 36, 78, and 134.

  Rationale: *To reflect the updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Updated DXA Scan with body composition to Week 78 and 134. Added footnote "e" to specify the window for obtaining DXA Scan with body composition.

  Rationale: *To reflect updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E). To clarify the permitted window for collection of DXA Scan with body composition.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Week 24 (Day 169), Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: added "free" to the scheduled biomarker sample of whole blood for cortisol.

  Rationale: *To clarify free cortisol is being tested on whole blood.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Week 24 (Day 169), Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: added footnote "i" on Biomarker sample: Whole blood for free cortisol, bone markers (BSAP, PINP, OC and CTX), ACTH, and TBNK to inform which visits these biomarker samples are scheduled to be collected.

  Rationale: *To reflect updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Updated HbA1c to Weeks 36, 48, 60, 72, 94, 118, 142, and 166.

  Rationale: *To reflect updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: updated Lipid profile to Weeks 36, 48, 60, 72, 94, 118, 142, and 166.

Rationale: *To reflect updated schedule of activities related to the LTE Period 2 as described in the Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Revised footnote "a" to describe requirements for urine pregnancy testing both at scheduled visits on-site and at home between visits if time between visits is longer than 1 month. Added timepoints for collection of HbA1c and lipid profile to the table and footnote "a" removed from HbA1c and lipid profile.

  Rationale: *To reflect updated schedule of activities related to the LTE Period 1 and 2 that requires urine pregnancy testing during the study at a minimum of monthly intervals and inform which visits the urine pregnancy tests can be collected on-site and which visits the urine pregnancy tests can be collected at home to ensure monthly urine pregnancy testing for females of childbearing potential. Timepoints for collection of HbA1c and lipid profile were added to the table, therefore this information was removed from the footnote.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Updated footnote "d" added language to inform that, if necessary, HBV DNA PCR may be tested at unscheduled visits.

  Rationale: *To inform that, if necessary, HBV DNA PCR test may be tested at unscheduled visits.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Added supervised training for study drug administration at home at Week 78 and corresponding footnote "f" to inform that if administration of study drug at home is not locally permitted or not opted by the subject, training for home administration is not required and that subjects not trained for administration of study drug at home will continue to receive study drug eow in the clinic.

  Rationale: *To ensure proper training for subjects which will be dosing at home during LTE Period 2 and clarify that if administration of study drug at home is not locally permitted or not opted by the subject, training for home administration is not relevant and dosing can continue to be performed at the clinic eow after Week 78 (during LTE Period 2).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Added Dispensation of study drug for home administration and corresponding footnote "g" to state study drug dispensation for home administration will start at Week 78 and is only applicable where locally permitted or opted by the subject, and that after Week 180 study drug will no longer be dispensed.

  Rationale: *To specify start and end of study drug dispensation for home administration and clarify study drug dispensation for home administration is only applicable where locally permitted or opted by the subject*.

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Added Subject

Diary Review and corresponding footnote "h" to inform that subjects who opted for dosing at home will have their diaries reviewed.

Rationale: *To inform that subjects who opted for home dosing during the LTE Period 2 will have their diaries reviewed at specified visits to capture dosing dates and times for dosing compliance.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Weeks 30, 36, 42, 48, 54, 60, 66, 72, 78, 86, 94, 102, 110, 118, 126, 134, 142, 150, 158, 166, 174: Added footnote "i" to inform the visit schedule for whole blood collection for free cortisol and bone markers.

  Rationale: *To align with Activity Schedule (Appendix E).*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Week 182 Final Study Visit: Removed of PGIC – FLARE and bone biomarkers; added HbA1c and lipid profile; added note "a" to inform that subjects who opted for dosing at home will have their diaries reviewed. Changed notes and b to b and c, respectively.

  Rationale: *PGIC – FLARE assessment at Week 178 will not be informative since it is based on the patient's recollection of disease activity at baseline and will continue to be collected at the Week 78 visit as previously planned. HbA1c and lipid profile were added to have a robust safety assessment at the updated final study visit at Week 182. To inform that subjects who opted for home dosing during the LTE Period 2 will have their diaries reviewed to capture dosing dates and times for dosing compliance. Footnotes b and updated to align with appropriate activities.*

- Operations Manual, Section 2.1 Individual Treatment Period Visits Activities Week 182 Final Study Visit: Added whole blood biomarker sample for free cortisol.

  Rationale: *Whole blood biomarker sample for free cortisol was added to have a robust safety assessment at the updated final study visit at Week 182.*

- Operations Manual, Section 2.2 Post-Treatment Activities: 30-Day Post-treatment Follow-up Phone Call was added, which includes an AE assessment and prior and concomitant medications assessment.

  Rationale: *Phone call was added to further ensure subject safety and capture of AEs/SAEs occurring early in the follow up period.*

- Operations Manual, Section 2.2 Post-Treatment Activities Post-Treatment Day 70 Visit: Added body weight, vital signs, whole blood biomarker sample for total and free cortisol, blood samples for serum conjugate ADC (serum), total antibody (serum), free A-1677770 (plasma) assays, and blood samples for serum ADA assays (including nAb), and ADA titer assays to the 70-day follow-up visit.

  Rationale: *To ensure more robust safety data collection at follow up. To ensure drug washout and assess immunogenicity during drug washout.*

- Operations Manual, Section 3.2, Re-Screening: Added wording "without prior AbbVie approval" regarding re-screening.

  Rationale: *To clarify the re-screening process.*

- Operations Manual, Section 3.5, Dual-Energy X-Ray Absorptiometry (DXA) Scan: Added collection of Z-score for evaluation of bone mineral density and instruction that measurements should be obtained from the distal forearm if neither the spine nor either hip are able to be scanned or interpreted. Added a Central Imaging Core Lab for central independent review of

DXA data and modified guidance for image acquisition. Removed performance of BMD and body composition assessment if DXA scan is not available.

Rationale: *To improve the robustness and interpretability of the DXA data collected. Other methods of BMD and body composition assessment are not interchangeable with DXA.*

- Operations Manual Section 3.15 Subject Dosing Diary: Added Operations Manual Section 3.15 Subject dosing diary to inform when the subjects will be dispensed a diary and the process of diary documentation and review.

  Rationale: *To inform subjects who opted for home dosing during LTE Period 2 and where locally permitted when they will receive a dosing diary, how they will be trained and how the dosing diary will be reviewed and properly documented.*

- Operations Manual, Section 3.16 Clinical Laboratory Tests, Table 1. Added Follicle Stimulating Hormone to the table to reflect changes in Protocol Section 5.2.

  Rationale: *Follicle Stimulating Hormone testing was added to align with addition of language in protocol section 5.2 which permits re-testing of FSH during study conduct.*

- Operations Manual, Section 3.16 Clinical Laboratory Tests, Pregnancy Tests (Serum and Urine): Updated language to align with the Protocol Section 5.2. Added "at investigator discretion Follicle Stimulating Hormone may be retested after the Screening visit."

  Rationale: *To align with language in Protocol Section 5.2 Contraception Recommendations which outlines requirements for females to be considered of non-childbearing potential. To align with addition of language in Protocol Section 5.2 which permits re-testing of FSH during study conduct.*

- Operations Manual, Section 3.16 Clinical Laboratory Tests, Pregnancy Tests (Serum and Urine): Added language to clarify requirements for serum and urine pregnancy testing during the study and add home urine pregnancy testing at a minimum of monthly intervals.

  Rationale: *To clarify requirements for serum and urine pregnancy testing during the study and add home urine pregnancy testing at a minimum of monthly intervals. Greater than monthly intervals between on-site visits in LTE Period 2 occur; thus, specific timepoints for serum and urine pregnancy testing are found in the Activity Schedule (Appendix E) and Operations Manual Section 2.1 Individual Treatment Period Visits Activities.*

- Operations Manual, Section 3.16 Clinical Laboratory Tests, Hepatitis Screening: Added language to Figure 1 to inform that HBV DNA PCR may be tested at unscheduled visits, if necessary.

  Rationale: *To provide instruction for subjects requiring HBV DNA PCR testing every 12 weeks to have an unscheduled visit to test HVB DNA PCR when planned visits are not at 12-week intervals.*

- Operations Manual, Section 3.16 Clinical Laboratory Tests, Tuberculosis Prophylaxis: Deleted duplicate "at least" and underscore between "rifampin must."

  Rationale: *To correct typographical errors.*

- Operations Manual, Section 3.16 Clinical Laboratory Tests, Hypersensitivity Testing: Simplified instructions for sample collection.

  Rationale: *To clarify that the laboratory manual provides all the instructions necessary for sample collection.*

- Operations Manual, Section 3.19 Home Healthcare Services after Week 24: Corrected spelling of healthcare.

  Rationale: *To correct the typographical error.*

- Operations Manual, Section 5.2 Treatment After End of Study: Updated last study visit to Week 182.

  Rationale: *To reflect the updated study design with the LTE Period 2.*

- Operations Manual, Section 6.1, Treatments Administered: Updated section to add paragraph detailing training requirements for subjects or designees on home administration of study drug and instructions for study drug administration for LTE Period 2.

  Rationale: *To provide guidance for training of subjects or designees on home administration of study drug and on-site and at home study drug administration for the LTE Period 2.*

- Operations Manual, Section 6.2, Packaging and Labeling: Removed statement that each syringe and carton will be labeled as required per country requirements.

  Rationale: *To remove redundant information.*

- Operations Manual, Section 6.4, Selection and Timing of Dose for Each Subject: Added instruction for handling of dosing of ABBV-154/placebo outside of the visit window.

  Rationale: *To provide guidance for minimal timing between doses in case of unanticipated out of window dosing to ensure subject safety.*