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Protocol for Study M20-370

Polymyalgia Rheumatica (PMR) Dependent on Glucocorticoid Treatment: A Randomized, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of ABBV-154

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FULL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Polymyalgia Rheumatica (PMR) Dependent on Glucocorticoid Treatment

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1 SYNOPSIS

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Polymyalgia Rheumatica (PMR) Dependent on Glucocorticoid Treatment	
Background and Rationale:	Glucocorticoids, such as prednisone/prednisolone, are the primary treatment for PMR and are highly effective at reducing inflammation and relieving pain. However, the administration of glucocorticoids is limited due to their long-term systemic side-effect profile including (but not limited to) hypothalamic-pituitary-adrenal (HPA) axis suppression, increased rates of bone fracture due to osteoporosis, cardiovascular effects, hyperglycemia, glaucoma, skin thinning, and weight gain. Therefore, once initial remission is achieved, glucocorticoids should be tapered gradually over time to minimize systemic side effects. Unfortunately, disease flares often occur while attempting to decrease the glucocorticoid dose, resulting in long-term glucocorticoid use and increased risk of glucocorticoid-related adverse events. Although the 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of PMR conditionally recommend use of methotrexate in addition to glucocorticoids in patients at high risk for relapse and/or prolonged therapy, there is a lack of strong efficacy data to support routine use of glucocorticoid-sparing agents in the treatment of PMR. In addition, the pathophysiology and disease mechanisms of PMR are not well delineated, leading to challenges in identifying potential therapeutic targets. While PMR symptoms are generally considered to reflect inflammation in synovial and periarticular structures, there is some indication that muscle pathology may also contribute. Some studies indicate elevated levels of plasma and serum tumor necrosis factor (TNF) and TNF in the muscle interstitium of symptomatic PMR patients. 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]. Binding of the adalimumab portion of the ABBV-154 ADC to activated immune cells that express transmembrane TNF is intended to deliver the anti-inflammatory payload intracellularly. The monoclonal antibody portion of the ADC provides targeted delivery, while the primary therapeutic mechanism of action in PMR is expected to be the intracellular GRM. Thus, ABBV-154 is a promising novel therapeutic agent for the treatment of PMR, hypothesizing that delivery of the GRM payload intracellularly would allow for control of PMR disease activity and discontinuation of systemic glucocorticoids, thereby avoiding further adverse effects caused by systemic glucocorticoid exposure.

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Objective(s) and Endpoint(s):	Primary Objective: To assess the safety and efficacy of ABBV-154 versus placebo in subjects with PMR, who are dependent on treatment with glucocorticoids with doses of at least 5 mg/day prednisone equivalent (glucocorticoid-dependent PMR). Secondary Objective: To assess the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ABBV-154. Primary Endpoint: Time to flare, where flare is defined as follows: • Presence of clinical signs and symptoms of PMR AND • Requirement to increase the glucocorticoid dose per investigator. Clinical signs and symptoms of PMR are defined as shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders that are not due to other causes. Secondary endpoints are listed as follows: • Achievement of flare-free state up to Week 24 • Cumulative glucocorticoid dose by 24 weeks • Change from Baseline in glucocorticoid dose at Week 24
Investigator(s):	Multicenter
Study Site(s):	Approximately 95 sites: Australia, Austria, Canada, France, Germany, Hungary, Italy, Japan, Netherlands, New Zealand, Poland, South Korea, Spain, United Kingdom, and United States
Study Population and Number of Subjects to be Enrolled:	160 adults with glucocorticoid dependent PMR
Investigational Plan:	This is a randomized, double-blind, placebo-controlled, multicenter, Phase 2 study in adults with PMR dependent on continuous use of glucocorticoids at the time of study entry. The study comprises a Screening Period up to 35 days, a 52-week double-blind Treatment Period, and a 70-day Follow-up Period after the last dose of study drug. Subjects will be randomized to one of 4 treatment arms in a 1:1:1:1 ratio to receive placebo administered subcutaneously (SC) or ABBV-154 administered SC as 40 mg every other week (EOW), 150 mg EOW, or 340 mg EOW. Randomization will be stratified by length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year), glucocorticoid dose at baseline (≥ 10 mg/day; < 10 mg/day prednisone equivalent), and enrollment in the optional PK sampling (yes; no). Starting at Baseline, each subject will switch from oral glucocorticoids obtained from independent sources to oral prednisone/prednisolone provided by the Sponsor at the equivalent dose that the subject was taking just prior to the Baseline Visit, rounded up to the nearest 1 mg. Beginning at Week 3, subjects will taper prednisone/prednisolone per

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	the protocol-defined glucocorticoid taper schedule to 0 mg prednisone equivalent by Week 24. If a subject has a suspected PMR flare at any time during the study, the flare should be confirmed according to the protocol defined flare definition as soon as possible, prior to initiating glucocorticoid rescue treatment. Once flare is confirmed, glucocorticoid rescue can be administered, with the dose and subsequent tapering at the discretion of the investigator, taking into consideration local standard of care, the subject's preflare and/or baseline dose, and not exceeding 15 mg/day. The Primary Analysis will be performed after all subjects have either completed the Week 24 visit or withdrawn from the study. The final analysis will be conducted after all subjects have either withdrawn from the study or completed Week 52 and the safety Follow-up Visit. The study sites and subjects will remain blinded until the final analysis is completed. A Wearable Device Substudy will enroll up to 96 subjects in select countries and sites where the digital health technology device is deployed and available. Subjects participating in this substudy will wear a watch-like digital device on the wrist that will collect data reflecting the subject's upper limbs range of motion (UL-ROM) and daily activity and sleep parameters.
Key Eligibility Criteria:	• Adults at least 50 years of age with a clinical diagnosis of PMR and fulfillment of the 2012 EULAR/ACR provisional classification criteria for PMR. • Following a confirmed diagnosis of PMR, subject must have shown a clinical response to prednisone (or equivalent). • Subject must have had at least 2 episodes of unequivocal PMR flare while attempting to taper prednisone, with the dose of prednisone (or equivalent) at the time of flare ≥ 5 mg/day, prior to Baseline; the most recent flare must have been within 24 weeks of Baseline. Unequivocal PMR flare is defined as clinical signs and symptoms of PMR (shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders) that resulted in an increase in glucocorticoid dose. • Subject must not exhibit clinical signs and symptoms of PMR (shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders) within 2 weeks of Baseline. • Subject must be on a stable prednisone (or equivalent) dose of 5 to 15 mg/day for ≥ 2 weeks prior to Baseline. Subjects may be on up to 25 mg/day at the Screening Visit provided that the subject is able to taper to 15 mg/day or less, with a stable dose ≥ 2 weeks prior to Baseline. • Subject must be willing to follow the protocol-defined glucocorticoid tapering regimen.

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Study Drug and Duration of Treatment:	ABBV-154 (40 mg EOW, 150 mg EOW, or 340 mg EOW) or matching placebo, administered SC. Duration of treatment is 52 weeks.
Date of Protocol Synopsis:	21 February 2022

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2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Polymyalgia rheumatica (PMR) is a relatively common inflammatory rheumatic disease occurring in adults age 50 years or older, manifesting as bilateral shoulder, hip, and neck pain and stiffness. Population-based studies examining the incidence of disease among residents of Olmsted County, Minnesota estimate the lifetime risk of developing PMR at 2.4% for women and 1.7% for men.[1] Worldwide, the incidence is highest in people of Northern European descent. The onset is typically abrupt or discrete in nature; morning stiffness is prominent, and bilateral shoulder pain is the initial symptom in most patients. Nonspecific symptoms such as fatigue, depression, anorexia, and sleep disturbance may also be present. The symptoms that PMR patients experience impacts physical function and performance of activities of daily living as well as psychological well-being.[2,3] Acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated in almost all patients and additional nonspecific laboratory findings such as anemia of chronic disease and thrombocytosis may also be present.[4] Approximately 16-21% of patients with PMR will develop giant cell arteritis (GCA), a separate but related inflammatory disease primarily affecting large vessels, at some point, and features of PMR are apparent in approximately 40-60% of patients diagnosed with GCA.[5]

Glucocorticoids, such as prednisone/prednisolone, are the primary treatment for PMR. The initial treatment recommendation is to begin the minimum effective glucocorticoid dose within a range of 12.5 to 25 mg/day prednisone equivalent.[6] The 2015 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of PMR provide a framework for glucocorticoid tapering but also emphasize that tapering schedules should be individualized based on regular monitoring of disease activity, laboratory markers, and adverse events (AEs).[6]

Glucocorticoids are highly effective at reducing inflammation and relieving pain. However, the administration of glucocorticoids is limited due to their long-term systemic side effect profile including (but not limited to) hypothalamic-pituitary-adrenal (HPA) axis suppression, increased rates of bone fracture due to osteoporosis, cardiovascular events, hyperglycemia, glaucoma, skin thinning, and weight gain. These adverse effects are generally dependent on dose, treatment time, concomitant and previous glucocorticoid intake, and individual sensitivity. Therefore, once initial remission is achieved, glucocorticoids should be tapered to minimize systemic side effects.[6] Unfortunately, disease flares often occur while tapering glucocorticoids, resulting in long-term glucocorticoid-associated morbidity.

Recent studies in patients with rheumatoid arthritis (RA) on glucocorticoids illustrate significant risks to patients even when used at low doses. In a retrospective cohort study, adults with RA on low-dose glucocorticoids (5 mg/day or less) had a statistically significant increase in the risk of hospitalized infection, similar to that seen in patients on biologic therapies in other studies.[7] A prospective cohort study of patients with RA with or without low-dose glucocorticoid treatment at least once during a follow-up period (median 10 years), showed patients with exposure to low-dose glucocorticoid experienced significantly more severe events (death, cardiovascular disease, severe infection, or

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fracture). The median duration of low-dose glucocorticoid treatment was 44.6 +/-40.1 months, and there was a time-dependent relationship between glucocorticoid treatment and the increased risk of these severe events.[8] In a population-based cohort analysis of 87,794 adults with six immune-mediated inflammatory diseases with no prior cardiovascular disease, including PMR patients (n = 25,581), the overall absolute risk of cardiovascular disease doubled after one year of using less than 5 mg prednisolone per day.[9]

Although the 2015 EULAR/ACR recommendations for the management of PMR conditionally recommend use of methotrexate in addition to glucocorticoids in patients at high risk for relapse and/or prolonged therapy, there is a lack of strong efficacy data to support routine use of glucocorticoid-sparing agents in the treatment of PMR.[6] In addition, the pathophysiology and disease mechanisms of PMR are not well delineated, leading to challenges in identifying potential therapeutic targets. While PMR symptoms are generally considered to reflect inflammation in synovial and periarticular structures, there is some indication that muscle pathology may also contribute[10,11] Some studies indicate elevated levels of plasma and serum tumor necrosis factor TNF[12,13] and TNF in the muscle interstitium of symptomatic PMR patients.[11]

ABBV-154 as Potential Treatment for PMR

Given the substantial negative systemic effects of glucocorticoids with long-term use, even at low dose, and the lack of strong evidence to support the routine use of glucocorticoid-sparing agents in PMR, there is a clear unmet need for new therapies that would allow PMR patients to stop using glucocorticoids and avoid glucocorticoid-related AEs.

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]. Binding of the adalimumab portion of the ABBV-154 ADC to activated immune cells that express transmembrane TNF is intended to deliver the anti-inflammatory payload intracellularly. The monoclonal antibody portion of the ADC provides targeted delivery, while the primary therapeutic mechanism of action in PMR is expected to be the intracellular GRM. Thus, ABBV-154 is a promising novel therapeutic agent for the treatment of PMR, hypothesizing that delivery of the GRM payload intracellularly would allow for control of PMR disease activity and discontinuation of systemic glucocorticoids, thereby avoiding further adverse effects caused by systemic glucocorticoid exposure.

2.2 Benefits and Risks to Subjects

The clinical efficacy of glucocorticoids in the treatment of PMR is well established. By utilizing expression of transmembrane TNF on activated immune cells, ABBV-154 has the potential to deliver an anti-inflammatory payload intracellularly, while minimizing systemic exposure to the free payload GRM. Based on the preclinical data discussed in the ABBV-154 Investigator's Brochure, ABBV-154 is expected to demonstrate a positive benefit-risk profile for the treatment of PMR.[14]

Medical review of the safety data from the Phase 1, single ascending dose study did not identify any unexpected risk or trend in the healthy volunteer population (including Japanese and Chinese subjects). For further details, please see the ABBV-154 Investigator's Brochure.[14]

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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 (AEs) associated with glucocorticoids include hypertension, HPA axis suppression, decreased bone formation, and cataract. Signs of infection, blood pressure changes, HPA axis function, 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, 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 with repeated doses up to 10 mg/kg intravenously, which is higher than the doses planned in this study, with consistent safety profile as labeled doses. 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 by 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 PMR with an acceptable benefit-risk profile for development in the treatment of this disease.

In view of the coronavirus – 2019 (COVID-19) pandemic, the benefit-risk profiles of various immunomodulatory therapies on COVID-19 are being evaluated. At this time, the effects of ABBV-154 on the course of COVID-19 are not well defined. Guidance regarding SARS CoV-2 vaccination is provided for investigators in Section 5.4.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective is to assess the safety and efficacy of ABBV-154 versus placebo in subjects with PMR, who are dependent on treatment with glucocorticoids with doses of at least 5 mg/day prednisone equivalent (glucocorticoid-dependent PMR).

- Primary Efficacy Objective: The primary efficacy objective of the study is to demonstrate that ABBV-154 treatment results in a longer disease-free time when compared with placebo treatment in the Intent-to-Treat (ITT) population, which consists of all randomized subjects with at least one dose of study drug.

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The hypothesis corresponding to the primary efficacy objective is that the time to flare with ABBV-154 treatment is longer than that with placebo treatment. The estimand for the primary endpoint is defined as the median time to flare in the study for each ABBV-154 group versus the placebo group in the ITT population. Subjects will be censored at the time of the last available assessment, initiation of immunomodulator, or violation of protocol-allowed systemic glucocorticoid use.

- Secondary Efficacy Objectives: The secondary efficacy objectives of the study are to demonstrate greater efficacy with ABBV-154 treatment when compared with placebo treatment 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 binary secondary endpoint: The difference in percentage of subjects achieving a response for each ABBV-154 group versus the placebo group in the ITT population.
  - For each continuous endpoint: The mean difference between each ABBV-154 group versus the placebo group in the ITT population.

Secondary

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

3.2 Primary Endpoint

The primary endpoint is the time to flare, where flare is defined as follows:

- Presence of clinical signs and symptoms of PMR

  AND

- Requirement to increase the glucocorticoid dose per investigator.

Clinical signs and symptoms of PMR are defined as shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders, as outlined in Section 5.7.

3.3 Secondary Endpoints

Secondary Endpoints

- Achievement of flare-free state up to Week 24
- Cumulative glucocorticoid dose by 24 weeks
- Change from Baseline in glucocorticoid dose at Week 24

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3.4 Additional Efficacy Endpoints

All secondary endpoints will be analyzed at all visits other than those listed. In addition, the following endpoints will be analyzed at all visits assessed, per Appendix F:

- Time to disease flare defined as Polymyalgia Rheumatica Activity Score (PMR-AS) increased from Baseline by ≥ 6.6.
  - PMR-AS = high-sensitivity CRP (hsCRP) (mg/dL) + Patient Assessment of Pain Severity (numeric rating scale [NRS], 0 – 10) + Physician Global Assessment of Disease Activity (NRS, 0 – 10) + (morning stiffness duration [MST] in minutes × 0.1) + elevation of upper limbs (EUL) (scale of 3 – 0)
- Time to disease flare defined as PMR-AS ≥ 9.35
- Achievement of PMR-AS < 1.5
- Achievement of PMR-AS < 7
- Achievement of ESR ≤ 30 mm/h at Week 24
- Achievement of hsCRP ≤ upper limit of normal (ULN) at Week 24
- Change from Baseline in hsCRP
- Change from Baseline in PMR-AS
- Change from Baseline in MST
- Change from Baseline in EUL
- Change from Baseline in Physician Global Assessment of Disease Activity NRS
- Change from Baseline in Patient Assessment of Pain Severity NRS
- Change from Baseline in Patient Assessment of Stiffness Severity NRS
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
- Change from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI)
- Change from Baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Item Bank v 1.0 – Sleep Disturbance
- Change from Baseline in Patient Assessment of Bruising Severity NRS
- Change from Baseline in EuroQol 5-dimension questionnaire, 5-level (EQ-5D-5L)
- Change from Baseline in Physician Assessment of Bruising Severity NRS
- For subjects participating in the Wearable Device Substudy:
  - Change from Baseline in the following sleep parameters: total sleep time, wake after sleep onset, sleep efficiency, and sleep onset latency
  - Change from Baseline in upper limbs range of motion (UL-ROM)

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3.5 Safety Measures

1. Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and AEs leading to discontinuation of 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 (predose) and at timepoints during the treatment period as specified in the Activity Schedule (Appendix F).

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 (predose) and at timepoints as specified in the Activity Schedule (Appendix F).

In addition, optional PK samples will be collected from approximately 32 subjects (approximately 8 subjects in each arm) who consent to participate in the optional PK sampling to provide additional data for PK characterization following repeated administrations. For these subjects, in addition to the standard sampling schedule, blood samples will also be collected at the following time points: Days 3, 4, 87, 88, 92 (Week 13) and 99 (Week 14).

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 F) throughout the study. The biomarkers to be analyzed include, but are not limited to:

- [redacted]
- [redacted]

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, ribonucleic acid [RNA], and deoxyribonucleic acid [DNA]) will be collected at specified time points (Activity Schedule, Appendix F) 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

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[redacted]

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study M20-370 is a randomized, double-blind, placebo-controlled, multicenter, 52-week Phase 2 study to assess the safety, tolerability, efficacy, PK, PD, and immunogenicity following multiple subcutaneous (SC) injections of ABBV-154 or placebo in 160 subjects with glucocorticoid-dependent PMR, as defined in Section 5.1.

The Screening Period may be up to 35 days. At the Baseline Visit, subjects will be randomized to one of 4 treatment arms in a 1:1:1:1 ratio, as follows: placebo administered SC in combination with a glucocorticoid taper or ABBV-154 administered as 40 mg every other week (EOW), 150 mg EOW, or 340 mg EOW in combination with a glucocorticoid taper. The glucocorticoid taper is identical for placebo and active treatment groups. Starting at Baseline, each subject will switch from oral glucocorticoids obtained from independent sources to oral prednisone/prednisolone provided by the Sponsor at the equivalent dose that the subject was taking just prior to the Baseline Visit, rounded up to the nearest 1 mg to a maximum of 15 mg. Beginning at Week 3, subjects will taper prednisone/prednisolone per the protocol-defined glucocorticoid taper schedule to 0 mg by Week 24 and remain off prednisone/prednisolone until the end of the Treatment Period, Week 52, unless a PMR flare is confirmed. A safety follow-up visit will be performed approximately 70 days after the last administration of ABBV-154/placebo.

If a subject has a suspected PMR flare at any time during the study, the flare should be confirmed according to the protocol-defined flare definition as soon as possible, prior to initiating glucocorticoid rescue treatment. Flare may be confirmed at either a scheduled visit or unscheduled visit. PMR must be confirmed as the cause of flare by eliminating other causes of the subject's symptoms/signs such as infection or other underlying disease. Once flare is confirmed at the visit, glucocorticoid rescue can be administered with the dose and subsequent tapering at the discretion of the investigator, taking into consideration local standard of care, the subject's preflare and/or baseline dose, and not exceeding 15 mg/day.

Addition of immunomodulators other than glucocorticoid rescue, as outlined above, are not permitted for rescue. If the investigator determines it is in the best interest of the subject to start an immunomodulator, the subject must discontinue study drug (ABBV-154/placebo and Sponsor-supplied prednisone/prednisolone; glucocorticoid will then be prescribed by the investigator as necessary, with dosing based on the investigator's judgement and in accordance with local standard of care).

The Primary Analysis will be performed after all subjects have either completed the Week 24 visit or withdrawn from the study. Interim analyses may be performed to reassess the treatment regimens in this study and to inform development of future studies.

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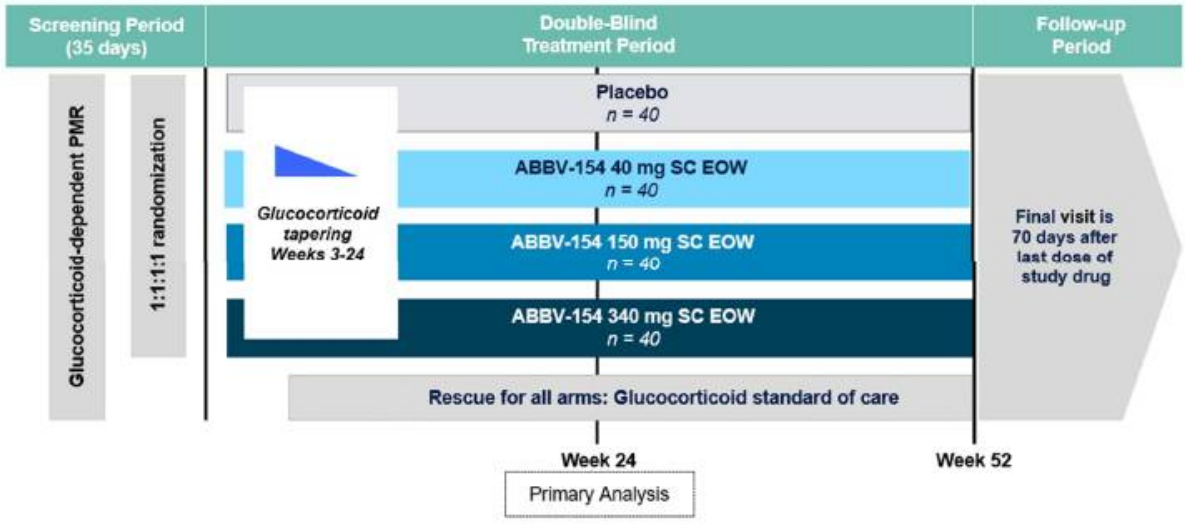
A final analysis will be conducted after all subjects have either withdrawn from the study or completed Week 52 and the safety Follow-up Visit. To maintain integrity of the trial, the study sites and subjects will remain blinded until the final analysis is completed. Selected AbbVie personnel may be unblinded to treatment assignment to conduct interim analyses or after an interim analysis to support regulatory interaction; details will be included in the interim unblinding plan (IUP).

Subjects in select countries and sites where the digital health technology device is deployed and available may also participate in a Wearable Device Substudy. Subjects participating in this substudy will wear a watch-like digital device on the wrist that will collect data reflecting the subject's UL-ROM and daily activity and sleep parameters (see Section 3.9 of the Operations Manual [Appendix H]). Enrollment will be capped at 96 subjects.

There will be optional serial photography for subjects who consent and at sites where photography is available.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix H). See Section 5.1 for information regarding eligibility criteria.

Figure 1. Study Schematic



EOW = every other week; PMR = polymyalgia rheumatica; SC = subcutaneous

4.2 Discussion of Study Design

Choice of Control Group

Placebo plus glucocorticoid taper (with taper duration dependent on baseline dose of glucocorticoid) 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. The control group in this study will follow the same glucocorticoid

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taper as the ABBV-154 treatment groups. Subjects are allowed to use glucocorticoid rescue if a PMR flare is confirmed, which is consistent with standard of care for PMR relapse.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The key efficacy measures in this study are standard for assessing disease activity in subjects with PMR. Additional exploratory efficacy measures were added in response to an unmet need for outcome assessments relevant to the PMR population based on literature review and consultation with PMR experts. Safety related measures, including clinical and laboratory procedures, in this study are standard and generally accepted for this study population.

Suitability of Subject Population

This study will enroll adult female and male subjects who are at least 50 years of age and have been diagnosed with PMR.[15] The study population is considered glucocorticoid-dependent. ABBV-154 has the potential to improve disease activity in PMR subjects while avoiding glucocorticoid-associated toxicity often seen with systemic glucocorticoids. While this is the first study to test ABBV-154 in PMR, safety results of ABBV-154 did not identify any unexpected risk or trend in the healthy volunteer population.

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 subjects on background methotrexate, in which ABBV-3373 demonstrated superiority over adalimumab based on comparison to a prespecified historical adalimumab mean.

The 3 SC dosing regimens (40 mg EOW, 150 mg EOW, and 340 mg EOW) selected for evaluation in this study 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. 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 payload 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 of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation. Additional information on screening (including re-screening) can be found in the Operations Manual (Appendix H).

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Consent

- 1. Subjects 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.

Demographics and Laboratory Assessments

- 2. Adult **male or female, at least** 50 years of age at the time of screening.
- 3. Body mass index (BMI) is ≥ 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.
- 4. **Laboratory values** must meet the following criteria within the Screening Period prior to the first dose of study drug:
  - Serum aspartate aminotransferase (AST) ≤ 2.5 × ULN;
  - Serum alanine transaminase (ALT) ≤ 2.5 × ULN;
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula ≥ 30 mL/min/1.73 m^2;
  - Absolute neutrophil count (ANC) ≥ 1,500/µL;
  - Absolute lymphocyte count ≥ 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 (TSH) < 10 mIU/L.
- 5. Subject must have a negative test result for anti-citrullinated protein (anti-CCP) at Screening.

Disease Activity

- 6. Clinical diagnosis of PMR and fulfillment of the 2012 EULAR/ACR provisional classification criteria for PMR (see Appendix D).[15] If utilizing the optional ultrasound criteria, ultrasound must have been assessed by a qualified physician experienced in musculoskeletal ultrasound.
- 7. Following a confirmed diagnosis of PMR, subject must have shown a clinical response to prednisone (or equivalent).
- 8. Subject must have had at least 2 episodes of unequivocal PMR flare while attempting to taper prednisone, with the dose of prednisone (or equivalent) at the time of flare ≥ 5 mg/day, prior to Baseline; the most recent flare must have been within 24 weeks of Baseline. Unequivocal PMR flare is defined as clinical signs and symptoms of PMR (shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders) that resulted in an increase in glucocorticoid dose.

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- 9. Subject must not exhibit clinical signs and symptoms of PMR (shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders) within 2 weeks of Baseline.

Subject History

- 10. Subject is judged to be in good health as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead ECG performed during Screening.
- 11. No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class. No history of anaphylactic reaction to any agent (e.g., food products and bee sting); or a reaction to any immunoglobulin G (IgG) containing product.
- 12. Subject must have no current or past history of infection including:
  - Active tuberculosis (TB) or meets TB exclusionary parameters (specific requirements for TB testing are provided in the Operations Manual);
  - 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;
  - Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the first dose of study drug;
  - Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
  - Confirmed COVID-19: 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 in symptoms;
  - Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high-risk behavior should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure;
- 13. Subjects must not have evidence of:
  - Hepatitis B virus (HBV): hepatitis B surface antigen (HBs Ag) positive (+) test or detectable HBV deoxyribonucleic acid (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): detectable HCV ribonucleic acid (RNA) in any subject with anti-HCV antibody (HCV Ab).
- 14. Subjects must not have any of the following medical diseases or disorders:

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- Suspected or confirmed adrenal insufficiency;
- Hypothyroidism for which the subject is not receiving physiologic replacement therapy;
- History of 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 mmHg at rest despite treatment;
- History of an organ transplant that requires continued immunosuppression;
- Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting, and/or aorto-coronary bypass surgery;
- History of GCA (based on clinical, ultrasound, and/or temporal artery biopsy diagnosis) or active symptoms (e.g., headache, temporal artery or scalp tenderness, jaw claudication, visual signs or symptoms, new or worsened extremity claudication) suggestive of GCA, per the investigator's judgement;
- History of systemic lupus erythematosus, systemic sclerosis, inflammatory myopathies;
- Active fibromyalgia;
- History of inflammatory arthritis (including but not limited to rheumatoid arthritis, psoriatic arthritis, etc.). A history of gout is permitted if subject has been both on stable (non-glucocorticoid) suppressive therapy and without flares for at least two years prior to Baseline and is expected to remain on this therapy through the end of study drug administration;
- History of glaucoma, osteonecrosis or osteoporosis with high risk of fracture (e.g., T-score ≤ –2.5 with history of fragility fracture);
- History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease;
- Active or suspected malignancy or history of any malignancy within the last 5 years, except for successfully treated nonmelanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix. Regardless of the time since remission, subjects with any history of lymphoma, leukemia, melanoma, or Merkel cell carcinoma;
- History of any medical condition other than PMR that is likely to require systemic glucocorticoid treatment during the study (e.g., asthma and chronic obstructive pulmonary disease [COPD] per investigator judgement). Inhaled glucocorticoids are allowed for stable medical conditions but must be at stable dose ≥ 4 weeks prior to Baseline.

15. Subject must not have a history of clinically significant (per investigator's judgment) drug or alcohol abuse within the 12 months prior to Baseline.

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- 16. 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. France only: Subjects must be registered with a social security scheme. Subjects may not fall within the scope of Article L1121-6 of the French Public Health Code (persons deprived of their freedom further to a judicial or administrative decision, persons receiving psychiatric care and persons admitted to a health and social facility for reasons unrelated to the study) or Article L1121-8 (adults under a legal protection order or unable to express their consent).
- 17. Wearable Device Substudy only: Subjects must not have a history of pre-existing sleep disorders, including insomnia, obstructive sleep apnea, restless leg syndrome or currently on prescription sleep medications to participate in the sleep assessment portion of the study. Subjects with these histories may participate in the study as a whole if all other eligibility criteria are met.

Contraception

- 18. For all 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 serum pregnancy testing at Baseline). Subjects with a borderline serum pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological causes of borderline results and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).
- 19. 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 70 days after the last dose of study drug (local practices may require 2 methods of birth control) (refer to Section 5.2 for more detail on contraception). Female subjects of non-childbearing potential do not need to use birth control. For France and 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.
- 20. Females must not be **pregnant, breastfeeding, or considering becoming pregnant** and may not donate eggs during the study or for approximately 70 days (150 days for France and UK only) after the last dose of study drug.
- 21. **If male**, and subject is **sexually active with a 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.
- 22. 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.

Concomitant Medications

- 23. Subject must be on a stable prednisone (or equivalent) dose of 5 to 15 mg/day for ≥ 2 weeks prior to Baseline. Subjects may be on up to 25 mg/day at the Screening Visit provided that the subject is able to taper to 15 mg/day or less, with a stable dose ≥ 2 weeks prior to Baseline.

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- 24. Subject must be willing to follow the protocol-defined glucocorticoid tapering regimen.
- 25. Subject must not have been treated with a prior TNF antagonist (adalimumab, etanercept, infliximab, certolizumab, golimumab).
- 26. Subject must not have prior exposure to ABBV-154.
- 27. Subject must have **discontinued use of immunomodulators other than prednisone (or equivalent) and hydroxychloroquine** prior to Baseline. Subject who is on current treatment with concomitant hydroxychloroquine must be on continuous treatment for ≥ 12 weeks and at stable dose (≤ 400 mg/day) for ≥ 4 weeks prior to Baseline and expected to remain on stable dose through the end of study drug administration. Prior to Baseline, subjects who need to discontinue immunomodulators to comply with this criterion are required to adhere to the washout periods specified below or at least 5 times the mean terminal elimination half-life of a drug. No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented.
  - ≥ 1 week for anakinra;
  - ≥ 4 weeks for methotrexate, sulfasalazine, hydroxychloroquine, cyclosporine, tacrolimus, bucillamine, iguratimod, azathioprine, mycophenolate, tocilizumab, sarilumab, and JAK inhibitors (upadacitinib, tofacitinib, baricitinib, filgotinib, ruxolitinib, peficitinib);
  - ≥ 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 or as per local label);
  - ≥ 8 weeks for abatacept;
  - ≥ 6 months for cyclophosphamide and other alkylating agents;
  - ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pretreatment level or normal reference range (local lab) if pretreatment levels are not available.
- 28. Subject must not have been treated with any intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, tendon sheath, or epidural glucocorticoids in the preceding 8 weeks prior to Baseline. Subjects must not have been treated with oral glucocorticoids for non-PMR reasons within 8 weeks prior to Baseline.
- 29. Subject must not have been treated with super-high potency and/or high potency topical glucocorticoids (see Appendix E) in the preceding 1 week prior to Baseline.
- 30. 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 Baseline or is currently enrolled in another interventional clinical study or was previously enrolled in this study.
- 31. Subject must not have received **any live vaccine** within 4 weeks (or longer if required locally) prior to Baseline, or expected need of live vaccination during study participation including at least 70 days after the last dose of study drug.

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- 32. Subject must have discontinued all opioid and analgesic medications with the exception of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, combination of acetaminophen with codeine, or combination of acetaminophen with hydrocodone ≥ 1 week prior to Baseline. Subjects entering on analgesics must be on stable dose ≥ 1 week prior to Baseline.
- 33. Subjects must not have been treated with oral traditional Chinese medicine within 4 weeks prior to Baseline.

5.2 Contraception Recommendations

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

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
     - Nonsurgical 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 (FSH) 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 France and 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 Study Day 1 (Baseline Visit).
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Study Day 1 (Baseline Visit).

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- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree to use male condoms, even if the male subject has undergone a successful vasectomy, from Study 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

Subjects must be able to safely discontinue any prohibited medications as specified in Section 5.1 and Section 5.4. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Intra-articular, intra-bursal, tendon sheath, trigger point or tender point, or epidural administration of glucocorticoids are not permitted prior to Week 24.

The following medications are prohibited through the end of study drug administration:

1. Systemic glucocorticoids (including but not limited to oral, intravenous, intramuscular), except as permitted as outlined in Section 5.1, Section 5.4, and Section 5.8.
2. Super-high potency and high potency topical glucocorticoids (see Appendix E).
3. Corticotropin gel injection (i.e., Acthar®)
4. Biologic Therapies: Subjects must have discontinued biologic therapies prior to the first dose of study drug as specified in the washout procedures (Eligibility Criterion 27 in Section 5.1). For all other biologic therapies, the required washout period is at least five times the mean terminal elimination half-life of the medication prior to Baseline. No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented. Therapies including but not limited to the following biologic therapies are prohibited medications through the end of study drug administration:

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- Abatacept
- Adalimumab
- Anakinra
- Belimumab
- Certolizumab
- Dupilumab
- Etanercept
- Golimumab
- Infliximab
- Ixekizumab
- Natalizumab
- Rituximab
- Risankizumab
- Sarilumab
- Secukinumab
- Tocilizumab
- Ustekinumab
- Vedolizumab

5. Conventional and targeted synthetic disease-modifying antirheumatic drugs (DMARDs): Subjects must have discontinued conventional and targeted synthetic DMARD therapies prior to Baseline as specified in the washout procedures (see Eligibility Criteria in Section 5.1), except for hydroxychloroquine. For all other conventional or targeted synthetic DMARDs, the required washout period is at least five times the mean terminal elimination half-life of the medication prior to Baseline.
6. Investigational drugs.
7. Live vaccination (see Section 5.4 for examples of live vaccines).
8. Any opiate analgesics with the exception of tramadol, combination of acetaminophen with codeine, or combination of acetaminophen with hydrocodone.
9. Traditional oral 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

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through the 70-day Post-treatment Follow-up Visit. Also, medications taken for PMR since the date of diagnosis and any glucocorticoids (based on subject's recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, dosage, route of administration and reason for discontinuation, if known.

Information regarding potential drug interactions with ABBV-154 can be located in the ABBV-154 Investigator's Brochure.[14]

Subjects should receive oral calcium and 25-hydroxy vitamin D and/or other therapy for prevention of glucocorticoid-induced osteoporosis in accordance with local standard-of-care practice, unless contraindicated, at the discretion of the investigator. Study participants with documented osteoporosis should be treated with approved drugs for osteoporosis according to local standard-of-care practice or clinical guidelines (e.g., National Osteoporosis Foundation or Japanese Society for Bone and Mineral Research).

See Section 5.8 for concomitant glucocorticoid treatment and rescue treatment for PMR flare.

Vaccines

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (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 (BCG);
- Typhoid (oral).

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.

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SARS CoV-2 Vaccination

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger RNA [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 blinded study drug (ABBV-154/placebo), 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 in patients with PMR 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 (Appendix H) for instructions on reporting any AEs associated with the COVID-19 vaccine.

Inhaled, Intraarticular, and Systemic Glucocorticoids

Inhaled glucocorticoids are allowed for stable medical conditions but must be at stable dose ≥ 4 weeks prior to the Baseline Visit and should remain stable throughout the study. Short-term use (≤ 14 days) of an inhaled glucocorticoid at an increased dose/frequency such as for treatment of an AE is allowed after Week 24 and should not exceed 2 episodes of short-term use through Week 52.

Short-term use (≤ 7 days) of systemic glucocorticoids (including oral, intravenous, intramuscular, intra-articular, intrabursal, tendon sheath, trigger point/tender point, or epidural administration) for non-PMR reasons such as treatment of an AE is allowed only after Week 24, provided the total cumulative dose from Week 24 through Week 52 does not exceed 100 mg prednisone equivalent.

Systemic glucocorticoid use for the treatment of PMR, including rescue therapy, is discussed in Section 5.8.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

NSAIDs and analgesics including 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. After Week 24, NSAID and analgesic dosing may be changed. Medication taken on an as-needed basis should not be taken within 24 hours prior to any study visit to avoid bias in outcome measurements.

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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 Area Medical Director (TA MD) 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 TA MD.
- Serious infections (e.g., sepsis) that cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk with continuation of study drug.
- Subject is noncompliant 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 TA MD.
- Subject is prematurely unblinded to study drug assignment by the investigator or AbbVie TA MD.
- Subject requires the addition of prohibited immunomodulatory medication for treatment of PMR.

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- Diagnosis of GCA.

When the blinded study drug (ABBV-154/placebo) is discontinued, the Sponsor-supplied prednisone/prednisolone must also be discontinued. Prednisone/prednisolone may then be prescribed by the investigator, with dosing based on the investigator's judgement and in accordance with local standard of care. Medications prescribed by the investigator should be documented on the concomitant medication eCRF.

Additional requirements related to abnormal laboratory values and selected specific AEs (safety topics of interest) are located in Section 6.2.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it may be 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 H.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored. Refer to the Operations Manual in Appendix H for details on how to handle study activities/procedures.

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 (except for visits that are intended only for study drug administration [Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50]), unless the subject has decided to discontinue the study participation entirely (withdrawal of informed consent). At the visits after study drug discontinuation, subjects should adhere to all study procedures except for dispensing of study drug and accountability, dosing diaries, and PK (conjugated ADC, total antibody, free A-1677770 assays) and immunogenicity (ADA assays) sample collection. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

If a subject prematurely discontinues study drug, 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.

In addition, a 30-day Follow-up Phone Call and 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

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Phone Call is not applicable for subjects who discontinued study drug prematurely and continued study participation with completion of at least 1 study visit that was at least 30 days after the last dose of study drug. This visit is not applicable for subjects who discontinued study drug prematurely and continued study participation with completion of at least 1 study visit that was 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.

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

5.7 Disease Activity and Flare Assessment

Assessment of PMR Signs and Symptoms

Subjects will be evaluated for PMR flare by the assessment of PMR signs and symptoms at study visits according to the schedule of assessments and the results entered into the eCRF. PMR signs and symptoms include the presence of any of the following:

- Shoulder and/or hip girdle pain with inflammatory stiffness
- Neck pain with inflammatory stiffness
- New or worsened limited range of motion of hips and/or shoulders

PMR must be confirmed as the cause of the clinical signs and symptoms in each subject by eliminating other causes such as infections, pre-existing medical conditions, and physical activity. Signs and symptoms due to causes other than PMR should not be entered into the eCRF or considered as PMR flare.

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Once clinical signs and symptoms of PMR are confirmed for a subject, the investigator should assess if an increase in glucocorticoid dose is required. If an increase in glucocorticoid dose is required, flare is confirmed and the subject should be offered glucocorticoid rescue as described in Section 5.8.

If a subject has a suspected flare at any time during the study, the flare should be confirmed as soon as possible (at a scheduled or unscheduled visit), prior to initiating glucocorticoid rescue treatment. Assessments at a visit where PMR flare is suspected must include assessment of PMR signs and symptoms, hsCRP, ESR, Patient Assessment of Pain Severity NRS, Physician Global Assessment of Disease Activity NRS, MST, EUL, UL-ROM and goniometer measurement for subjects in the Wearable Device Substudy, AE assessment, and concomitant therapy. Additional assessments may be added per the investigator's medical judgement.

Other Disease Activity Assessments

Disease activity will also be assessed through collection of the ESR, PMR-AS components (i.e., hsCRP, Patient Assessment of Pain Severity NRS, Physician Global Assessment of Disease Activity NRS, MST, and EUL), and UL-ROM and goniometer measurement for subjects in the Wearable Device Substudy at study visits as noted in the Activity Schedule (Appendix F) and at any visit where PMR flare is suspected. Further details can be found in the Operations Manual (Appendix H).

5.8 Study Drug

ABBV-154 and Matching Placebo

ABBV-154 and matching placebo will be manufactured and provided by AbbVie (Table 1). Each dose will be administered by a healthcare professional as 3 SC injections (2 prefilled syringes [PFS] with 1.5 mL fill volume and 1 PFS with 0.4 mL fill volume) in the abdomen or thigh. Blinded study drug will be administered EOW at approximately the same time of day, preferably between 7 and 11 a.m., beginning on Day 1 (Baseline Visit). The study drug can be taken with or without food. A 15- to 30-minute observation period is required after each dose. The last dose of ABBV-154/placebo will be given at Week 50.

ABBV-154 and matching 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°C) 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 study drug for the subject. Study drug is for investigational use only and will only be used for the conduct of this study.

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Table 1. Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
ABBV-154	Solution for Injection/infusion in PFS	40 mg 150 mg	subcutaneous	AbbVie
Placebo for ABBV-154	Solution for Injection/infusion in PFS	Not applicable	subcutaneous	AbbVie

PFS = prefilled syringe

Glucocorticoids

Starting at the Baseline Visit, all subjects will switch from oral glucocorticoids obtained from independent sources to open-label oral prednisone/prednisolone provided by the sponsor at the same dose they were taking just prior to the Baseline Visit, rounded up to the nearest 1 mg to a maximum of 15 mg. At the Baseline Visit (Day 1), the subject may take non-sponsor provided oral glucocorticoid at the required dose prior to randomization so that the subject does not have to delay the usual time of glucocorticoid dosing. If a subject has already taken the glucocorticoid dose at home on the day of the Baseline Visit, dosing should not be repeated with sponsor-provided prednisone/prednisolone. Open-label prednisone/prednisolone will be self-administered orally (PO) once per day (QD) (Table 2). The baseline dosage will be administered QD until the Week 3 visit, at which time tapering will begin as described in Section 6.1 of the Operations Manual (Appendix H). Glucocorticoids should be stored as specified on the label (may differ by manufacturer and local requirements) in a secure location.

Table 2. Non-Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Prednisone/ Prednisolone	Tablets	1 mg, 5 mg, and 10 mg	Oral	Generic[a]

a. Prednisone/prednisolone may be supplied by AbbVie per local requirements.

If a subject or home health nurse (if utilizing home care visits) is unable to come to the study site to pick up their study drug due to COVID-19 or other reasons, a direct-to-patient study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable.

Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit; study site personnel will document compliance.

Glucocorticoid Tapering Schedule

Starting at Week 3, prednisone/prednisolone will be tapered to 0 mg prednisone/prednisolone per day according to the schedule in Section 6.1 of the Operations Manual (Appendix H), based on the glucocorticoid dosage at Baseline. The glucocorticoid taper will be completed by Week 24 for all subjects.

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Rescue Treatment for PMR Flare

If a subject has a suspected PMR flare at any time during the study, the flare should be confirmed as soon as possible, prior to initiating glucocorticoid rescue treatment. Flare may be confirmed at either a scheduled visit or unscheduled visit. Assessments performed at a visit for suspected flare are listed in Section 5.7 and in the Operations Manual (Appendix H). Additional assessments may be added per the investigator's medical judgement. PMR must be confirmed as the cause of flare by eliminating other causes of the subject's symptoms/signs such as infection or other underlying disease. Once flare is confirmed, glucocorticoid rescue should be administered with the dose and subsequent tapering at the discretion of the investigator, taking into consideration local standard of care, the subject's preflare and/or baseline dose, and not exceeding 15 mg/day. The investigator must record his/her recommendation to increase the prednisone/prednisolone dose due to PMR flare in the eCRF, regardless of whether or not the subject agrees to increase his/her dose. The specific dose of glucocorticoid rescue therapy taken by the subject should be documented in the eCRF.

While receiving open-label rescue treatment with prednisone/prednisolone, the subject should continue in the study and receive blinded study drug (ABBV-154/placebo) unless the subject meets the study drug discontinuation criteria (see Section 5.5).

If a subject remains on prednisone/prednisolone up to the Week 52 visit, the subject will take the last dose of Sponsor-supplied prednisone/prednisolone on the day prior to the Week 52 or on the day of the Week 52 visit and may restart individually-sourced prednisone equivalent on or after the day of the Week 52 visit, under the medical guidance of the investigator.

Addition of immunomodulators other than glucocorticoid rescue, as outlined above, are not permitted for rescue. If the investigator determines it is in the best interest of the subject to start an immunomodulator, the subject must discontinue study drug treatment (ABBV-154/placebo and sponsor-supplied prednisone/prednisolone). Any subsequent medications prescribed by the investigator should be documented on the concomitant medication eCRF.

5.9 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. Subjects will be randomized to either placebo or ABBV-154 administered SC as 40 mg EOW, 150 mg EOW, or 340 mg EOW in a 1:1:1:1 ratio.

Randomization will be stratified by the following:

- Glucocorticoid use at Baseline: ≥ 10 mg/day; < 10 mg/day prednisone equivalent
- Length of prior glucocorticoid treatment for PMR: ≤ 1 year; > 1 year
- Enrollment in optional PK sampling: yes; no

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the

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subject will remain blinded to each subject's treatment throughout the study. Selected AbbVie personnel may be unblinded to treatment assignment after an interim analysis to support regulatory interactions; details will be included in the IUP. To maintain the blind, the ABBV-154 and placebo prefilled 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.

In the event of a medical emergency that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Subject Unblinding by Site transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email (global.helpdesk@cenduit.com). For country-specific phone numbers, please see the following website: http://www.cenduit.com.

In the event the blind is broken before notification to the AbbVie TA MD, the AbbVie TA MD should be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on appropriate eCRF.

5.10 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 the IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.11 Data Monitoring and Adjudication Committees

Data Monitoring Committee

An external data monitoring committee (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 further describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications.

Adjudication Committee

An independent Adjudication Committee will be established to adjudicate potentially glucocorticoid-related 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.

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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, meet protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

Since the primary endpoint for this study is time to PMR flare, these endpoint events (shoulder and/or hip girdle pain with inflammatory stiffness, neck pain with inflammatory stiffness, or new or worsened limited range of motion of hips and/or shoulders that are not due to other causes) will not be collected as AEs unless they fulfill criteria for an SAE or result in a fatal outcome. Expected manifestations of PMR that constitute worsening of the underlying condition are not to be recorded as AEs.

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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 preplanned 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** **Confirmed ALT or AST > 3 × ULN**	Hepatic eCRF
Renal impairment **Renal dysfunction** **Renal failure** **Confirmed serum creatinine >1.5 × 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 aminotransferase; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; MACE = major adverse cardiac event; SAE = serious adverse event; ULN = upper limit of normal

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

Death of Subject — An event that results in the death of a subject.

Life-Threatening — An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

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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 treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 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 AEs 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 IMP in accordance with global and local requirements.

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AEs 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 AEs (NCI CTCAE Version 5.0.[16]), which can be accessed at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug ABBV-154 (or matching placebo) and prednisone/prednisolone:

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

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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

Where "study drug" is used in this toxicity management section, study drug refers to blinded ABBV-154/placebo.

The management of specific AEs (safety topics of interest) and laboratory parameters are presented below.

For subjects who discontinue study drug but continue study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central 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. If a subject is taking prednisone/prednisolone, it should not be stopped for the surgery.

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 postdose 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 3.19, Hypersensitivity Testing (Appendix H).

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

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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 hyperglycemia with appropriate standard of care.

Management of GCA

Subjects should be closely monitored for the development of symptoms of GCA (e.g., headache, temporal artery or scalp tenderness, jaw claudication, visual signs or symptoms, new or worsened extremity claudication). If a subject is diagnosed with GCA during the course of the study, the subject must be discontinued from ABBV-154/placebo and Sponsor-supplied prednisone/prednisolone, and the investigator must ensure the subject is promptly treated and followed appropriately for GCA per local 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 assessment and management should follow local standard of care, which may include measuring cortisol levels and/or ACTH stimulation testing 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.

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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 apply to blinded study drug (ABBV-154/placebo), and may require a supplemental eCRF to be completed (Section 6.1). For subjects with ongoing laboratory abnormalities which 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 which 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, 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 (ANC)	If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its BL value. Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
Absolute lymphocyte count (ALC)	If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its BL value.
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.

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Laboratory Parameter	Toxicity Management Guideline
AST or ALT	Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5. A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from BL). • 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 BL 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).
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 restart 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).

Ab = antibody; ALC = absolute lymphocyte counts; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BL = baseline; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; eCRF = electronic

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case report form; HB = hepatitis B; HBs = hepatitis B surface; 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 performed after all subjects have either completed the Week 24 visit or withdrawn from the study.

The final analysis will be conducted after all subjects have either withdrawn from the study or completed Week 52 and the safety Follow-up Visit. To maintain integrity of the trial, the study sites and subjects will remain blinded until the final analysis is completed. Selected AbbVie personnel may be unblinded to treatment assignment after an interim analysis to support regulatory interactions and future development decisions; details will be included in the IUP.

7.2 Definition for Analysis Populations

The following population will be used for the efficacy analysis:

- Intent-to-Treat (ITT) Population: The ITT Population includes all subjects who were randomized and received at least 1 dose of study drug. The ITT Population will be analyzed as randomized (i.e., according to the randomized treatment assignment).

The following population will be used for the safety analysis:

- Safety Population: The Safety Population includes all subjects who were randomized and received at least 1 dose of study drug. The Safety Population will be analyzed as treated (i.e., according to the actual treatment received).

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

Primary endpoint:

- Subjects will be censored at the time of immunomodulator initiation or violation of protocol-allowed systemic glucocorticoid use.

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Categorical secondary endpoints:

- Subjects will be considered as not achieving the response after the initiation of rescue medication, immunomodulator or violation of protocol-allowed systemic glucocorticoid use.

Continuous endpoint:

- No intercurrent event will be considered in the analysis of glucocorticoid dose.

7.4 Statistical Analyses for Efficacy

Efficacy analysis will be performed by the subject's randomized treatment group. All statistical tests will be performed at a 2-sided significance level of 0.1. A 95% confidence interval (CI) of the treatment difference between each ABBV-154 dose and placebo will be provided. The actual value of stratification factors will be used in the analysis. Enrollment in the optional PK sampling is not expected to impact any of the efficacy endpoints and will thus not be used as a stratification factor in the analysis.

- For time-to-event endpoints, comparison of number of events will be made between each ABBV-154 dose and placebo based on log-rank test stratified by stratification factors. The point and CI estimate of median time to event and event-free rate for each group will be reported based on Kaplan-Meier curves. Hazard ratio and its corresponding CI for each ABBV-154 group compared with placebo will be estimated using Cox regression analysis adjusting for stratification factors. For all analyses of time-to-event endpoints, subject without an event at the time of the analysis will be administratively censored at the time of the last available assessment.
- For categorical variables, pairwise comparison will be made between each ABBV-154 dose and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for stratification factors. Nonresponder imputation incorporating multiple imputation (NRI-MI) to handle COVID-19 will be the primary approach to handle missing data for categorical endpoints.
- For continuous variables other than glucocorticoid dose, the comparison will be made between each ABBV-154 dose and placebo based on the mixed effect model repeated measures (MMRM) adjusting for visit, interaction between treatment and visit, actual values of stratification factors as fixed factors, and baseline value as a covariate. The MMRM will be the primary approach to handle missing values for continuous endpoints.
- For analyses of glucocorticoid dose, comparison will be made between each ABBV-154 dose and placebo based on the analysis of covariance (ANCOVA) adjusting for stratification factors as fixed factors, and baseline glucocorticoid dose as a covariate.

Summary and Analysis of the Primary Endpoints

The primary endpoint is the time to flare. The time origin is the first dose of study drug and the time of first flare will be use for the analysis. Comparison of the primary endpoint will be made between each ABBV-154 dose and placebo using the log-rank test adjusting for stratification factors. The point and CI estimate of median time to flare and flare-free rate for each group will be reported based on Kaplan-

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Meier curves. Hazard ratio and its corresponding CI for each ABBV-154 group versus placebo will be estimated using Cox regression analysis adjusting for stratification factors.

One supplementary analysis for the primary endpoints is to test a prespecified set of dose-response models among ABBV-154 dose groups and the placebo group at Week 24 using the Multiple Comparison Procedure – Modeling (MCP-Mod) method.

Summary and Analysis of Secondary Endpoints

Analysis of secondary endpoints are described above.

Summary and Analysis of Additional Efficacy Endpoints

Analysis of additional efficacy endpoints are described above.

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 (≥ 10 mg/day; < 10 mg/day prednisone equivalent)
- Length of prior glucocorticoid treatment for PMR (≤ 1 year; > 1 year)
- Age (≤ median; > median)
- Sex (female; male)
- Race (white; nonwhite)

In addition, change from Baseline in glucocorticoid dose at Week 24 will be analyzed by the following subgroup:

- Glucocorticoid status at Week 24 (glucocorticoid free; not glucocorticoid free)

7.5 Statistical Analyses for Safety

All safety analyses will be performed using the Safety Population, as defined in Section 7.2. Data will be analyzed based on the actual treatment subjects received. TEAEs, laboratory assessments, and vital signs will be summarized. Details will be described in the SAP.

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 Medical Dictionary for Regulatory Activities (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 also be provided. Pretreatment AEs will be summarized separately.

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For selected laboratory parameters, a listing of all subjects with any laboratory value that is Grade ≥ 3 of NCI CTCAE 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 Analyses for Pharmacokinetics and Immunogenicity

Concentrations of conjugated ADC, total antibody, and free payload (A-1677770) will be summarized for 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.

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

7.7 Statistical Analyses for Biomarker Data

7.8 Interim Analysis

Interim analyses may be performed to reassess the treatment regimens in this study and to inform development of future studies.

7.9 Overall Type I Error Control

Overall Type I error control is not planned in this Phase 2 study.

7.10 Sample Size Determination

A total of 37 flares in the highest dose of ABBV-154 group and placebo group would provide more than 90% power to detect a hazard ratio of 0.296 at 2-sided significance level of 0.1. The hazard ratio of 0.296 is determined under the assumption that flares would occur during the tapering and within 12 weeks after the end of tapering (up to Week 36), and 70% and 30% of subjects will remain flare-free by Week 36 in the highest dose of ABBV-154 group and placebo group, respectively.

Based on an E_{max} model with ED_{50} of 150 mg, a total of 74 flares are expected for the Primary Analysis. A sample size of 40 subjects in each of the ABBV-154 and placebo arms is planned to ensure appropriate accrual of flares. A sample size re-estimation may be considered at an interim analysis prior to unblinding of the study team. The sample size increase will be capped at approximately 100 subjects.

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8 ETHICS

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

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

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

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

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currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

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

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

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

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
[redacted]	[redacted]
ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADC	Antibody-drug-conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
Anti-CCP	Anti-citrullinated protein
AST	Aspartate aminotransferase
BAP	Bone-specific alkaline phosphatase
BL	Baseline
BMD	Bone mineral density
BMI	Body mass index
[redacted]	[redacted]
BUN	Blood urea nitrogen
CH50	Total hemolytic complement
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
COPD	Chronic obstructive pulmonary disorder
COVID-19	Coronavirus – 2019
CPK	Creatinine phosphokinase
CRP	C-reactive protein
[redacted]	[redacted]
CXR	Chest x-ray
D	Day
DMARD	Disease-modifying antirheumatic drug
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DXA	Dual-energy x-ray absorptiometry
E4W	Every 4 weeks

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ECG	Electrocardiogram
eCRF	Electronic case report form
ED_{50}	Dose that produces half of E_{max}
EDC	Electronic data capture
E_{max}	Maximum effect attributable to the drug
EOW	Every other week
ePRO	Electronic patient-reported outcome
ESR	Erythrocyte sedimentation rate
EUL	Elevation of upper limbs
EULAR	European League Against Rheumatism
EQ-5D-5L	EuroQol 5-dimension questionnaire, 5-level
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
FSH	Follicle-stimulating hormone
GCA	Giant cell arteritis
GCP	Good clinical practice
GFR	Glomerular filtration rate
GRM	Glucocorticoid receptor modulator
HAQ-DI	Health Assessment Questionnaire Disability Index
HAV	Hepatitis A virus
HB	Hepatitis B
HbA1c	Glycated hemoglobin
HBc	Hepatitis B core
HBc Ab	Hepatitis B core antibody
HBc Ab+	Hepatitis B core antibody positive
HBs	Hepatitis B surface
HBs Ab	Hepatitis B surface antibody
HBs Ab+	Hepatitis B surface antibody positive
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	HCV antibody
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal

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hsCRP	High-sensitivity C-reactive protein
IA	Interim analysis
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IgG	immunoglobulin G
IgE	immunoglobulin E
IMP	Investigation medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-Treat
IUD	Intrauterine device
IUP	Interim unblinding plan
IUS	Intrauterine hormone-releasing system
LCMS	Liquid chromatography-mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MACE	Major adverse cardiac event
MCP-Mod	Multiple Comparison Procedure – Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Model Repeated Measurements
mRNA	Messenger ribonucleic acid
MST	Morning stiffness
nAb	Neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMSC	Nonmelanoma skin cancer
NRI-MI	Nonresponder imputation incorporating multiple imputation
NRS	Numeric rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
[redacted]	[redacted]
[redacted]	[redacted]
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PFS	Prefilled syringe(s)

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PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PMR	Polymyalgia rheumatica
PMR-AS	Polymyalgia Rheumatica Activity Score
PO	Orally
PPD	Purified protein derivative
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QD	Once daily
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction(s)
SC	Subcutaneous
SF-8b	Short Form 8b
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UL-ROM	Upper limbs range of motion
US	Ultrasound
VAS	Visual analog scale
W	Week
WBC	White blood cell

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-370: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Polymyalgia Rheumatica (PMR) Dependent on Glucocorticoid Treatment

Protocol Date: 21 February 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)

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APPENDIX C. 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 & Pharmacometrics

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APPENDIX D. PMR CLASSIFICATION CRITERIA

The 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) provisional classification criteria for PMR are shown below.[15]

PMR Classification Criteria Scoring Algorithm – Required Criteria: Age 50 years or older, bilateral shoulder aching and abnormal CRP and/or ESR[a]		
	Points without US (0 – 6)	**Points with US[b] (0 – 8)**
Morning stiffness duration > 45 minutes	2	2
Hip pain or limited range of motion	1	1
Absence of RF and anti-CCP antibody	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	1

Anti-CCP = anti-citrullinated protein; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PMR = polymyalgia rheumatica; RF = rheumatoid factor; US = ultrasound

a. A score of 4 or more is categorized as PMR in the algorithm without US and a score of 5 or more is categorized as PMR in the algorithm with US.

b. Optional US criteria.

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APPENDIX E. SUPER-HIGH POTENCY AND HIGH POTENCY TOPICAL GLUCOCORTICOIDS

Potency	Generic Name(s)	Brand Name(s)	Vehicle Type(s)	Strength (%, except as noted)
Super-high	Clobetasol proprionate	Clobex	Lotion	0.05
		Temovate	Cream, gel, ointment	0.05
		Temovate E	Cream, emollient base	0.05
		Olux-E, Tovet	Foam	0.05
		Cormax	Solution	0.05
	Betamethasone dipropionate, augmented	Diprolene	Gel, lotion, ointment (optimized)	0.05
	Halobetasol proprionate	Ultravate	Cream, lotion, ointment	0.05
	Fluocinonide	Vanos	Cream	0.1
	Diflucortolone valerate	Nerisone Forte	Ointment, cream	0.3
	Flurandrenolide	Cordran	Tape	4 mcg/sq cm
High	Betamethasone diproprionate	Diprolene AF	Cream, augmented formulation	0.05
		Diprosone	Ointment	0.05
	Clobetasol proprionate	Impoyz	Cream	0.025
	Halobetasol proprionate	Bryhali	Lotion	0.01
	Desoximetasone	Topicort	Cream, ointment, spray	0.25
		Topicort	Gel, cream	0.05
	Diflorasone diacetate	ApexiCon, Florone	Ointment, cream	0.05
		ApexiCon E	Cream, emollient	0.05
	Fluocinonide	Lidex	Cream, gel, ointment, solution	0.05
	Halcinonide	Halog	Cream, ointment, solution	0.1
	Amcinonide	Cyclocort, Amcort	Ointment	0.1

Source: Ference 2009[17], National Psoriasis Foundation[18]

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APPENDIX F. ACTIVITY SCHEDULE

The following table shows the required activities for subjects throughout the study.

The individual activities are described in detail in the **Operations Manual** (Appendix H). Modifications allowed due to COVID-19 are detailed in the Operations Manual.

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Study Activities Table

Activity	Screening	Baseline	Optional PK	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Optional PK	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wks 26 – 52[a]		Unscheduled for flare evaluation[b]	Premature Discontinuation	30-Day Follow-up Phone Call	70-Day Follow-up Visit
	D -35 to Day 1	y	y	D 8	D 15	D 29	D 43	D 57	D 71	D 85	Days 87, 88, 92	D 99	D 113	D 127	D 141	D 155	D 169	EOW Vi it	E4W Vi it				
INTERVIEWS & QUESTIONNAIRES																							
Subject information and informed consent	✓																						
Eligibility criteria	✓	✓																					
Medical/surgical history	✓	✓																					
Alcohol and nicotine use	✓																						
Adverse event assessment	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tuberculosis risk assessment questionnaire	✓																						
Health Assessment Questionnaire Disability Index (HAQ-DI)		✓				✓		✓		✓			✓		✓		✓		✓		✓		
Patient Assessment of Pain Severity numeric rating scale (NRS)		✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
PROMIS® Item Bank v 1.0 – Sleep Disturbance		✓				✓		✓		✓			✓		✓		✓		✓		✓		
Morning stiffness duration (MST)		✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
Patient Assessment of Bruising Severity NRS *Weeks 36 and 52		✓								✓							✓		✓*		✓		

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Activity	Screening	Baseline	Optional PK	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Optional PK	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wks 26 – 52[a]		Unscheduled for flare evaluation[b]	Premature Discontinuation	30-Day Follow-up Phone Call	70-Day Follow-up Visit
	Day –35 to Day 1	Day 1	Days 3, 4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Days 87, 88, 92	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E4W Visits				
EuroQol 5-dimension questionnaire, 5-level (EQ-5D-5L)		✓				✓		✓		✓			✓		✓		✓		✓		✓		
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)		✓				✓		✓		✓			✓		✓		✓		✓		✓		
Patient Global Impression of Severity (PGIS) in Pain, Stiffness and Physical Function		✓				✓		✓		✓			✓		✓		✓		✓		✓		
Patient Global Impression of Change (PGIC) in Pain, Stiffness, and Physical Function (*Week 52)																	✓		✓*		✓		
Dispense wearable device (substudy)[c]		✓	Subject wears the device and performs UL-ROM at home during the 1st hour after getting out of bed each day for 1 week after each site visit with UL-ROM assessment (Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36[c])																				
Collect wearable device (substudy) (*Week 38 or 40; **If discontinuing all study participation)																		✓	✓*		✓ **		
Dispense electronic patient-reported outcome (ePRO) handheld device		✓	Subject Completes Daily Diary for Pain and Stiffness Severity NRS; daily Day 1 - Week 52																				
Collect ePRO handheld device (*Week 52)																			✓*		✓		
LOCAL LABS & EXAMS																							
Body weight (*Weeks 36 and 52)	✓	✓				✓		✓		✓			✓		✓		✓		✓*		✓		✓

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Activity	Screening	Baseline	Optional PK	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Optional PK	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wks 26 – 52[a]		Unscheduled for flare evaluation[b]	Premature Discontinuation	30-Day Follow-up Phone Call	70-Day Follow-up Visit
	Day –35 to Day 1	Day 1	Days 3, 4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Days 87, 88, 92	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E4W Visits				
Height	✓																						
Vital signs	✓	✓		✓	✓	✓		✓		✓			✓		✓		✓		✓		✓		✓
Physical exam	✓	✓								✓							✓		✓		✓		
12-lead electrocardiogram (*Week 52)	✓																✓		✓*		✓		
Chest x-ray	✓																						
Dual-energy x-ray absorptiometry scan (*Week 52)	✓																		✓*				
Assessment of PMR signs and symptoms		✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
Physician Global Assessment of Disease Activity NRS		✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
Elevation of upper limbs (EUL)		✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
Upper limbs range of motion (UL-ROM) and goniometer measurement (substudy)[c]		✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
Physician Assessment of Bruising Severity NRS (*Weeks 36 and 52)		✓								✓							✓		✓*		✓		
Photographic documentation of bruising (subjects who consent)		✓								✓							✓						
Erythrocyte sedimentation rate (ESR)	✓	✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		

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Activity	Screening	Baseline	Optional PK	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Optional PK	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wks 26 – 52[a]		Unscheduled for flare evaluation[b]	Premature Discontinuation	30-Day Follow-up Phone Call	70-Day Follow-up Visit
	Day –35 to Day 1	Day 1	Days 3, 4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Days 87, 88, 92	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E4W Visits				
Urine pregnancy test (females of childbearing potential)		✓				✓		✓		✓			✓		✓		✓		✓		✓		✓
CENTRAL LABS																							
Serum pregnancy test (females of childbearing potential); FSH if applicable	✓																						
High-sensitivity C-reactive protein (hsCRP)	✓	✓				✓		✓		✓			✓		✓		✓		✓	✓	✓		
Hematology (*Weeks 28, 36, 44, and 52)	✓	✓				✓		✓		✓			✓		✓		✓		✓*		✓		✓
Glycated hemoglobin (HbA1c) (*Weeks 36 and 52)	✓									✓							✓		✓*				✓
Clinical chemistry (*Weeks 28, 36, 44, and 52)	✓	✓				✓		✓		✓			✓		✓		✓		✓*		✓		✓
Lipid profile (*Weeks 36 and 52)		✓								✓							✓		✓*				
Urinalysis	✓	✓				✓		✓		✓			✓		✓		✓		✓		✓		
Thyroid-stimulating hormone (TSH)	✓																						
Tuberculosis (TB) Test (QuantiFERON TB Gold test and/or local purified protein derivative [tuberculin] skin test)	✓																						
Human immunodeficiency virus (HIV); hepatitis B virus (HBV) and hepatitis C virus (HCV) (Note: HBV	✓																						

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Activity	Screening	Baseline	Optional PK	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Optional PK	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wks 26 – 52[a]		Unscheduled for flare evaluation[b]	Premature Discontinuation	30-Day Follow-up Phone Call	70-Day Follow-up Visit
	Day –35 to Day 1	Day 1	Days 3, 4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Days 87, 88, 92	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E4W Visits				
DNA PCR every 12 weeks where required)																							
Rheumatoid factor, anti-citrullinated protein (anti-CCP) antibody	✓																						
25-hydroxyvitamin D		✓																					
Beta-D-glucan (Japan only)	✓																						
Blood samples for conjugated antibody-drug-conjugate (ADC) (serum), total antibody (serum), free A-1677770 (plasma) assays (predose on dosing days)		✓		✓	✓	✓		✓		✓			✓		✓		✓		✓		✓		✓
Blood samples for anti-drug antibody (ADA) assays (including ADA titer and neutralizing antibody [nAb]) (predose on dosing days)		✓				✓		✓		✓			✓		✓		✓		✓		✓		✓
Optional pharmacokinetic (PK) assessments			✓								✓	✓											
[redacted]																							

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Activity	Screening	Baseline	Optional PK	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Optional PK	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wks 26 – 52[a]		Unscheduled for flare evaluation[b]	Premature Discontinuation	30-Day Follow-up Phone Call	70-Day Follow-up Visit
	Day –35 to Day 1	Day 1	Days 3, 4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Days 87, 88, 92	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	EOW Visits	E4W Visits				
[redacted]																							
℞ TREATMENT																							
Randomization/drug assignment		✓																					
Blinded study drug (ABBV-154/placebo) administration (*last dose is Week 50)		✓			✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓*				
Dispense prednisone/prednisolone with dosing diary and dosing instructions[d]		✓			✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓			
Review and copy prednisone/prednisolone dosing diary; monitor compliance					✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Perform study drug reconciliation					✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓*	✓	✓		

a. Weeks 26 to 52: EOW (every other week) designates Weeks 26, 30, 34, 38, 42, 46, and 50; whereas, E4W (every 4 weeks) designates Weeks 28, 32, 36, 40, 44, 48, and 52.

b. Unscheduled visit for flare assessment must include the noted assessments at a minimum; additional assessments may be done at the discretion of the investigator.

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c. Subjects in Wearable Device Substudy to wear digital device for 1 week after each site visit with UL-ROM assessment (Baseline and Weeks 4, 8, 12, 16, 20, 24, 28, 32, and 36). Daily activity and sleep parameters will be measured. Subject performs UL-ROM at home during the 1st hour after getting out of bed each day for specified weeks. Subject will perform UL-ROM and goniometer assessments at site visits indicated.

d. If prednisone/prednisolone is required for rescue treatment, it will be dispensed after PMR flare is confirmed (see Section 5.8). Subjects should record all rescue prednisone dosing on the prednisone/prednisolone dosing diary. If a subject remains on prednisone/prednisolone rescue treatment up to Week 52, the last dose of Sponsor-supplied prednisone/prednisolone will be taken one day prior to the Week 52 visit and individually-sourced prednisone equivalent may be restarted the day of the Week 52 visit, under the medical guidance of the investigator. If necessary, the subject may take sponsor provided prednisone/prednisolone (from Week 50 dispensation) on the day of the Week 52 visit so subject does not have to delay the usual time of glucocorticoid dosing.

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APPENDIX G. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	13 May 2021
Version 2.0	13 July 2021
Version 2.1 (UK only)	29 September 2021
Version 2.2 (France only)	19 October 2021
Version 2.3 (Germany only)	23 November 2021

The purpose of this version is to update the following sections below. In addition, minor typographical 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 including Figure 1, Section 5.9, Randomization/Drug Assignment; Section 7.10, Sample Size Determination; Operations Manual, Section 6.3, Method of Assigning Subjects to Treatment Groups: Changed the randomization ratio from 2:1:1:1 to 1:1:1:1 and the total subjects to be enrolled from 200 to 160.

  Rationale: To reduce the proportion of placebo subjects to match the number of subjects in each ABBV-154 dose group. Reduction in the number of placebo patients maintains the power for the primary endpoint.

- 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, Investigational Plan; Protocol Section 4.1, Overall Study Design and Plan and Operations Manual Section 3.9, Wearable Device Substudy: Changed the enrollment cap for the Wearable Device Substudy from 120 to 96.

  Rationale: To align with the change in the randomization ratio and the reduction of number of subjects in the placebo arm.

- Protocol Section 1, Synopsis, Key Eligibility Criteria; Protocol Section 4.2, Discussion of Study Design and Section 5.1, Eligibility Criteria: Deleted upper age limit of 80 (criterion #2).

  Rationale: To align the study population with the known epidemiology of PMR.

- Protocol Section 1, Synopsis, Investigational Plan; Protocol Section 5.1, Eligibility Criteria: Deleted dosage specifications for clinical response to prednisone or equivalent from criterion #7.

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Rationale: To align with 2015 EULAR/ACR treatment recommendations and real-world practice, which may include intramuscular injections of glucocorticoid with initial higher doses > 25 mg/d prednisone equivalent.

- Protocol Section 3.6, Pharmacokinetic and Immunogenicity Endpoints: Changed the number of subjects needed for collecting the optional PK samples from approximately 40 to approximately 32 subjects (approximately 8 subjects in each arm).

  Rationale: To align with the change in the randomization ratio and the reduction of number of subjects in the placebo arm.

- Protocol Section 4.1, Overall Study Design and Plan and Operations Manual, Section 3.9 Wearable Device Substudy: Removed requirement to participate in the Wearable Device Substudy as a condition for overall study participation in subjects who otherwise qualify for the Substudy.

  Rationale: To allow subjects the option to participate in the main study in the case they do not choose to participate in the Wearable Device Substudy.

- Protocol Section 4.1, Overall Study Design and Plan and Figure 1, and Section 7.8, Interim Analysis: Modified plan for Interim analyses.

  Rationale: To reduce the number of planned interim analyses to reassess the treatment regimens in this study and to inform the development of future studies and allow flexibility in interim analysis timing to account for variability in the observed enrollment rate.

- Protocol Section 5.1, Eligibility Criteria: Updated history of GCA to specify a diagnosis may be based on clinical, ultrasound, and/or temporal artery biopsy.

  Rationale: To clarify the definition of history of GCA considered exclusionary for this study, for which diagnosis may be established clinically, or by ultrasound and/or temporal artery biopsy even if clinical symptoms of GCA were not present.

- Protocol Section 5.1, Eligibility Criteria: Changed criterion #14 to exclude active fibromyalgia.

  Rationale: To allow subjects with inactive fibromyalgia to participate in the study, as inactive fibromyalgia is not considered a confounder and will not affect subject safety.

- Protocol Section 5.1, Eligibility Criteria: Moved wording in criterion #14 regarding inflammatory arthritis to a new bullet and added wording to allow subjects with stable gout to participate in the study.

  Rationale: The bullet was reorganized to address inflammatory arthritis in a separate point from other rheumatic diseases excluded. To allow subjects with stable gout to participate in the study, as stable gout controlled on suppressive therapy and without recent flare is not expected to interfere with interpretation of PMR flare and will not affect subject safety.

- Protocol Section 5.1, Eligibility Criteria: Revised criterion #14 requirements related to current and prior malignancy.

  Rationale: To allow subjects with a remote history (> 5 years) of malignancy to participate in the clinical trial but continue to exclude potential subjects with a history of specific malignancies consistent with the warnings section of the adalimumab Summary of Product Characteristics.

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- Protocol Section 5.1, Eligibility Criteria: Added wording to criterion #16 for France only regarding requirement for subjects to be registered with a social security scheme and that subjects may not fall within the scope of Article L1121-6 and Article L1121-8 of the French Public Health Code.

  Rationale: To align with French regulations.

- Protocol Section 5.1, Eligibility Criteria and 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 19) (France and UK only) and for males (criterion 21) (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 20) (France and UK only), and males must not consider fathering a child or donating sperm for 150 days after last dose of study drug administration (criterion #22) (UK only).

  Rationale: The duration of contraception, pregnancy, and egg/sperm donation requirements after last dose of study drug was changed for France and 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 five times the upper limit of the mean elimination half-life, using the most conservative estimate of the half-life among the three 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, Criterion #27; Section 5.3 Prohibited Medications and Therapy: Added language to permit hydroxychloroquine use at a stable dose.

  Rationale: Allow use of hydroxychloroquine at stable dose as it is not expected to impact study efficacy assessments or subject safety.

- Protocol Section 5.1, Eligibility Criteria: For criterion #27, added sulfasalazine to the list of immunomodulators requiring washout prior to Baseline.

  Rationale: Washout of 4 weeks was specified for sulfasalazine as it was previously omitted.

- Protocol Section 5.1, Eligibility Criteria: For criterion #30, added the word "interventional" to describe clinical study.

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

- Protocol Section 5.1, Eligibility Criteria: For criterion #31, 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 five times the upper limit of the mean elimination half-life of subcutaneously administered ABBV-154.

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- 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: Deleted sentence stating that prohibited medications could be used to treat AEs when no medical alternative is available.

  Rationale: To clarify that use of a prohibited medication is considered prohibited at any time as specified in Section 5.3.

- Protocol Section 5.5, Withdrawal of Subjects and Discontinuation of Study: Added language to clarify that AbbVie may prematurely discontinue the study at any time, including discontinuing 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 "or rule out safe continuation of the study drug" to abnormal laboratory result reason for study discontinuation.

  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; Appendix F, Activity Schedule; Operations Manual Section 2.4, Individual Post-Treatment Period Visit Activities: Added a phone call to the subject to assess AEs/SAEs at 30 days after the last dose of study drug.

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

- 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, clarified when to re-start study drug after surgery, and added guidance to continue prednisone/prednisolone in a subject who undergoes surgery.

  Rationale: To ensure subject safety by providing instructions for interruption of study drug before and after surgery. To clarify that prednisone should not be held for surgery to prevent adrenal insufficiency in subjects who have been on long-term systemic glucocorticoid therapy.

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- Protocol Section 6.2, Toxicity Management: Added sentence 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 Section 7.1, Statistical and Analytical Plans: Added text to describe that interim analysis will support future development decisions.

  Rationale: To clarify the reason for interim unblinding should it occur.

- Protocol Section 7.10, Sample Size Determination: Changed the sample size from 200 subjects total to 40 subjects in each of the ABBV-154 and placebo arms.

  Rationale: To reflect the change in randomization ratio and clarify the sample size calculation was based on subjects per arm rather than total number of subjects.

- Protocol Section 7.10, Sample Size Determination: Changed the total number of flares from 64 to 37 for the highest dose and placebo arms and from 101 to 74 for all treatment arms combined.

  Rationale: The expected total number of flares is reduced as the result of changing the randomization ratio and sample size.

- Protocol Section 7.10, Sample Size Determination: Revised the timing of the possible sample size re-estimation to be at one interim analysis to occur prior to unblinding of the study team.

  Rationale: To align with modifications to remove specific timing and number of planned interim analyses and clarify that sample size re-estimation will occur before the study team is unblinded.

- Protocol Appendix A, Study Specific Abbreviations and Terms: Corrected the terms for hepatitis surface antibody abbreviation.

  Rationale: To correct a typographical error.

- Protocol Appendix C, List of Protocol Signatories: Updated list of protocol signatories.

  Rationale: Administrative change.

- Protocol Appendix F, Activity Schedule: Added additional column for the 30-day follow-up phone call to assess adverse events and prior/concomitant therapy and added "Visit" to 70-day follow-up column header.

  Rationale: Added a 30-day follow-up call and clarified that the 70-day follow-up is a visit to ensure all treatment-emergent AEs/SAE have been resolved.

- Protocol Appendix F, Activity Schedule (including footnote c); Operations Manual, Section 2.1 Individual Treatment Period Visit Activities (footnotes); Operations Manual, Section 3.9 Wearable Device Substudy: Reduced the duration of time during which subjects participating in the Wearable Device Substudy wear the device.

  Rationale: To limit data collection for this substudy to the one week after site visits at which UL-ROM is performed to reduce subject burden and increase subject compliance to substudy procedures.

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- Protocol Appendix F, Activity Schedule; Operations Manual Section 2.4, Individual Post-Treatment Period Visit Activities: Added body weight and vital signs collection to 70-day follow-up visit.

  Rationale: To ensure more robust safety data collection at follow up.

- Protocol Appendix F, Activity Schedule; Operations Manual Section 2.1 Individual Treatment Period Visit Activities and Section 3.19, Clinical Laboratory Tests, Table 1: Added collection of 25-hydroxyvitamin D to the Baseline Visit and to Table 1, Clinical Laboratory Tests.

  Rationale: To collect additional data on subjects Baseline status which may affect bone mineral density.

- Protocol Appendix F, Activity Schedule; Operations Manual Section 2.4, Individual Post-Treatment Period Visit Activities: Added PK and immunogenicity sample collection at the 70-day Follow-Up Visit.

  Rationale: To ensure drug washout and assess immunogenicity during drug washout.

- Operations Manual, Section 1, Contacts: Updated Clinical Lab and Biomarker Sample Storage contact information.

  Rationale: Administrative change.

- Operations Manual, Section 2.1, Individual Treatment Period Visit Activities: All individual study day headers were updated to include an additional column.

  Rationale: Added for alignment with the 30-day phone call column in the Study Activity Table.

- Operations Manual, Section 2.1, Individual Treatment Period Visit Activities: For screening visit, changed reference for Section 3.6 to 3.5, describing chest x-ray.

  Rationale: To correct typographical error.

- Operations Manual, Section 2.2 Premature Discontinuation Visit, Footnote b: Footnote was removed.

  Rationale: Footnote was not applicable to the premature discontinuation visit anymore since subjects no longer wear the device continuously.

- Operations Manual Section 3.2, Rescreening: Added additional opportunity for rescreening of subjects with the AbbVie Therapeutic Area Medical Director/Scientific Director approval.

  Rationale: To allow subjects who have already been screened twice the opportunity to rescreen on a case-by-case basis, if appropriate.

- Operations Manual Section 3.2, Rescreening: Added FSH to the list of testing not required to be repeated if rescreening a subject within 14 days from the sample collection date of the previous screen.

  Rationale: To reduce unnecessary procedures, as FSH would not be expected to change significantly in 14 days.

- Operations Manual Section 3.6, 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 the spine nor either hip are able to be scanned or

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interpreted. Added a Central Imaging Core Lab for central independent review of DXA data and modified guidance for image acquisition.

Rationale: To improve the robustness and interpretability of the DXA data collected.

- Operations Manual Section 3.8, Patient-Reported Outcomes, Patient Global Impression of Severity (PGIS): Corrected upper limit of scoring scale and verbal anchors.

  Rationale: To correct typographical errors and omissions in upper limit of scoring scale and verbal anchors.

- Operations Manual Section 3.9, Wearable Device Substudy, Daily Activity and Sleep Assessment at Home: Added instruction for when subjects are to press the event marker.

  Rationale: To provide clarity on when the assessment is to be completed.

- Operations Manual, Section 3.14, Vital Signs: Added language to specify that blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes to replace deleted sentence "measurements should be assessed consistently throughout the study."

  Rationale: To provide clarity and ensure consistency of the procedure used to assess blood pressure and pulse, which can be affected by positional changes and activity.

- Operations Manual Section 3.20, Subject Withdrawal from Study: Added language to specify that subjects discontinued from study drug and continuing study participation no longer follow rescue treatment parameters.

  Rationale: To clarify that rescue treatment does not apply to subjects discontinued from study drug and continuing study participation.

- Operations Manual 3.22 Home Healthcare Service: Added option for home healthcare visits provided by a study nurse or third-party vendor beginning with Week 6.

  Rationale: To provide greater flexibility for study subjects.

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