abbvie

Protocol for Study M16-852

Giant Cell Arteritis: Phase 3 Safety and Efficacy Study of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA

VERSION:	7.0	DATE:	31 May 2023
SPONSOR:	AbbVie Inc.*	NUMBER OF SITES:	Approximately 140
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EU CT:	2023-505476-29-00

FULL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA

Incorporating Versions 1.0, 2.0, 2.1 (VHP), 3.0, 4.0, 5.0, 6.0, 7.0, and Administrative Changes 1 and 2.

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted]
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064, USA

Mobile: [redacted]
Email: [redacted]
EMERGENCY 24 hour Number: +1 973-784-6402

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

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

abbvie

TABLE OF CONTENTS

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

LIST OF TABLES

LIST OF FIGURES

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

LIST OF APPENDICES

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1 SYNOPSIS

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA	
Background and Rationale:	Giant cell arteritis (GCA), also known as temporal arteritis, is a systemic vasculitis of the large vessels with a predilection for the cranial branches of the aorta. The course of GCA is characterized by a relatively abrupt onset followed by chronic vascular and systemic inflammation. Corticosteroid (CS) therapy is the current mainstay of treatment for GCA. Though many symptoms resolve rapidly with initiation of high dose CS therapy, there are cases reported of chronic underlying vascular inflammation and progression of vascular pathology despite control of clinically apparent disease activity. Thus, there remains the potential for improved treatment options which can mitigate this subclinical vascular inflammation. Recent studies of tocilizumab, a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, have demonstrated superiority in the achievement of GCA disease remission compared to standard-of-care CS therapy. Upadacitinib is a novel Janus kinase 1 (JAK1) inhibitor currently being developed for the treatment of adult patients with inflammatory diseases. The enhanced selectivity of upadacitinib may have the potential for an improved benefit/risk profile by mitigating JAK2 inhibitory effects on erythropoiesis and myelopoiesis. It is hypothesized that inhibition of cytokine signaling through the IL-6, Interferon-gamma (IFN-γ), and IL-12 signaling pathways by upadacitinib will result in improved ability to maintain remission with absence of GCA signs and symptoms compared to placebo (PBO), even in a setting of a rapid reduction of CS therapy.
Objectives and Endpoints:	**Objectives** Period 1: To evaluate the efficacy of upadacitinib 7.5 mg once daily (QD) and 15 mg QD in combination with a 26-week CS taper regimen compared to PBO in combination with a 52-week CS taper regimen, as measured by the proportion of subjects in sustained remission at Week 52, and to assess the safety and tolerability of upadacitinib in subjects with GCA. Period 2: To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1. **Endpoints** Primary endpoint: the proportion of subjects achieving sustained remission at Week 52. Sustained remission is defined as having achieved both of the following: • Absence of GCA signs and symptoms from Week 12 through Week 52 • Adherence to the protocol-defined CS taper regimen.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

	Multiplicity-controlled secondary endpoints include: 1. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52. Sustained complete remission is defined as having achieved all of the following: • Absence of GCA signs and symptoms from Week 12 through Week 52; • Normalization of erythrocyte sedimentation rate (ESR) (to < 30 mm/hr) (if ESR ≥ 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52; • Normalization of high sensitivity C-reactive protein ([hsCRP] to < 1 mg/dL without elevation [on 2 consecutive visits] to ≥ 1 mg/dL) from Week 12 through Week 52; and • Adherence to the protocol-defined CS taper regimen. 2. Cumulative CS exposure through Week 52. 3. Time to first disease flare through Week 52. Disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement > 30 mm/hr (attributable to GCA), AND requiring an increase in CS dose. 4. Proportion of subjects who experience at least 1 disease flare through Week 52. 5. Proportion of subjects in complete remission at Week 52. Complete remission is defined as having achieved all of the following: • Absence of GCA signs and symptoms; • Normalization of ESR (to < 30 mm/hr); if ESR ≥ 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met; • Normalization of hsCRP to < 1 mg/dL and • Adherence to the protocol-defined CS taper regimen. 6. Proportion of subjects in complete remission at Week 24. 7. Change from Baseline in the 36-item Short Form Quality of Life Questionnaire (SF-36) Physical Component Score (PCS) at Week 52. 8. A group of four endpoints: • Number of disease flares per subject through Week 52. • Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) at Week 52. • Assessment of Treatment Satisfaction Questionnaire for Medication (TSQM) patient global satisfaction subscale at Week 52. • Rate of CS-related adverse events (AEs) through Week 52.
Investigators:	Multicenter

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Study Sites:	Approximately 140 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 420 subjects with a diagnosis of active GCA will be enrolled; a minimum of 30% of subjects with new onset disease and up to 70% of subjects with relapsing disease will be enrolled. The study will also allow enrollment of up to 20% of subjects with previous use of an IL-6 inhibitor with discontinuation based on reasons other than disease flare.
Investigational Plan:	The study duration will include a 35-day maximum Screening Period: a 52-week randomized, double-blind, parallel-group treatment period (Period 1); a 52-week, blinded extension period in which subjects may either be re-randomized or continue in their original treatment assignment (Period 2); and a 30-day follow-up period. Period 1 (52 weeks): Subjects who meet eligibility criteria will be randomized in a 2:1:1 ratio to 1 of 3 treatment groups: • Upadacitinib 15 mg QD + 26-week CS taper regimen (n = 210) • Upadacitinib 7.5 mg QD + 26-week CS taper regimen (n = 105) • PBO QD + 52-week CS taper regimen (n = 105) All subjects will receive CS (prednisone or prednisolone) ≥ 20 mg QD at Baseline. The initial dose will be at the discretion of the investigator, based on disease severity and comorbid medical conditions, and will be tapered according to a predefined schedule over a 26- or 52-week period. Open -label prednisone or prednisolone will be provided until the dose is tapered to 20 mg/day. Subsequently, blinded prednisone or prednisolone will be provided for the remaining blinded taper regimen. Period 2 (52 weeks): Subjects assigned to either dose of upadacitinib who achieved sustained remission for at least 24 consecutive weeks prior to the Week 52 visit (at the end of Period 1) will be re-randomized in a 2:1 ratio to either continue on upadacitinib or switch to PBO in Period 2. Subjects who achieved remission for at least 24 weeks prior to the Week 52 visit (at the end of Period 1) who were assigned to PBO in Period 1 will continue to receive PBO in Period 2. Remission is defined as absence of GCA signs and symptoms, AND adherence to the protocol-defined CS taper regimen or CS-free. At Week 52, subjects who have absence of GCA signs and symptoms AND are CS-free, but do not meet the above remission criteria will continue in Period 2 on their originally randomized treatment assignment. All other subjects will be discontinued from study drug at the end of Period 1.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Key Eligibility Criteria:	Eligible subjects will be adults, ≥ 50 years of age at the Screening Visit, who meet the following criteria:
	• Diagnosis of GCA according to the following criteria:
	  • Adult male or female, at least 50 years of age
	  • History of ESR ≥ 50 mm/hour or hsCRP/CRP ≥ 1.0 mg/dL
	  • Presence of at least one of the following:
	  • Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication), or
	  • Unequivocal symptoms of polymyalgia rheumatica ([PMR] shoulder and/or hip girdle pain associated with inflammatory morning stiffness).
	  • Presence of at least one of the following: temporal artery biopsy revealing features of GCA or evidence of large vessel vasculitis by angiography or cross-sectional imaging (such as magnetic resonance imaging [MRI], computed tomography [CT] or positron emission tomography [PET]), assessed by a qualified radiologist experienced in evaluating large vessel vasculitis, or ultrasound of temporal arteries assessed by a qualified physician experienced in evaluating large vessel vasculitis.
	• Active new onset or relapsing GCA with active disease within 8 weeks of Baseline. Active disease is defined by the presence of at least one of the following: unequivocal cranial symptoms of GCA, unequivocal symptoms of PMR, or other features judged by the investigator to be consistent with GCA or PMR flares, AND an ESR ≥ 30 mm/hr or hsCRP/CRP ≥ 1 mg/dL.
	• Subjects must have received treatment with ≥ 40 mg prednisone (or equivalent) at any time prior to Baseline and be receiving prednisone (or equivalent) ≥ 20 mg QD at Baseline.
	• Subjects must have GCA that, in the opinion of the investigator, is clinically stable to allow the subject to safely initiate the protocol-defined CS taper regimen.

Study Drug and Duration of Treatment:	• Upadacitinib, 15 mg tablet oral, 52 or 104 weeks duration • Upadacitinib, 7.5 mg tablet oral, 52 or 104 weeks duration • Placebo corresponding to upadacitinib, tablet oral, 52 or 104 weeks duration • Prednisone/Prednisolone and corresponding PBO, tablet oral or capsule oral, 52-week duration
Date of Protocol Synopsis:	31 May 2023

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Giant Cell Arteritis (GCA)

Giant cell arteritis (GCA), also known as temporal arteritis, is a systemic vasculitis of the large vessels with a predilection for the cranial branches of the aorta. GCA affects women to men in a 3:1 ratio and almost exclusively those over age 50. The course of GCA is characterized by a relatively abrupt onset followed by chronic vascular and systemic inflammation. Left untreated, patients with GCA tend to manifest persistent systemic and vascular inflammation with resultant pathology related to progressive vascular occlusion.

The characteristic symptoms of GCA include those related to vascular occlusion such as headache, jaw pain related to use (jaw claudication), as well as ocular symptoms. Visual symptoms occur in up to 30% of GCA patients and can include diplopia or vision loss with 15% of patients manifesting permanent unilateral or bilateral loss of vision. Patients with GCA experience systemic symptoms such as fever, fatigue, and weight loss. There is a significant overlap between GCA and polymyalgia rheumatica (PMR) with up to 30% of those with GCA manifesting PMR.

Corticosteroid (CS) therapy is the current mainstay of treatment for GCA. High doses of CS therapy are initially required and most often quickly control inflammation and prevent vision loss and/or other irreversible symptoms. Initial high dose CS therapy is followed by a prolonged period of dose tapering. During this tapering phase, between 50% and 80% of GCA patients experience a disease flare.[1] In addition to symptomatic pathology, prolonged exposure to CS therapy results in approximately 80% of GCA patients manifesting steroid-associated pathology within 10 years following diagnosis.[2]

Though many symptoms such as headache and PMR symptoms resolve rapidly with initiation of high dose CS therapy, ischemic complications such as jaw claudication may take considerably longer. Additionally, GCA is associated with chronic vascular damage including aortic inflammation with subsequent aortic aneurysm formation which may result in spontaneous rupture and/or the need for surgical repair. Notably, there are cases reported of chronic underlying vascular inflammation and progression of vascular pathology despite control of clinically apparent disease activity, even while still on chronic CS therapy.[3] Thus, there remains the potential for improved treatment options which can mitigate this subclinical vascular inflammation.

The prevalence of GCA varies by region with reported rates of temporal arteritis/GCA varying widely between 1 and 30 per 100,000 individuals and with further enrichment in individuals ≥ 50 years of age. The highest rates are observed in populations from Scandinavian countries and of Northern European descent.[1]

The current treatment regimen for GCA consists almost exclusively of CS therapy. Numerous trials of biologic and non-biologic immunosuppressants have attempted to identify steroid-sparing therapies, but until recently none have been definitively successful. Recently, Phase 2 and Phase 3 studies of tocilizumab have demonstrated superiority in the achievement of GCA disease remission compared to

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

standard-of-care CS therapy.[4,5] In addition to increased rates of remission, these studies demonstrated the ability to reduce exposure to CS therapy by nearly half with concomitant tocilizumab treatment.]

Upadacitinib as Potential Treatment for GCA

Targeting the Janus kinase (JAK) signaling pathway for autoimmune diseases such as GCA, rheumatoid arthritis (RA), Crohn's disease (CD), psoriatic arthritis (PsA), ulcerative colitis (UC), atopic dermatitis (AD), and axial spondyloarthritis (AxSpA), is supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. The activation of JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation which contribute to multiple inflammatory and autoimmune disorders, including the key cytokines driving GCA pathogenesis.[6-8]

The JAK family is composed of 4 members: JAK1, 2, 3, and tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases act in tandem to activate the Signal Transducer and Activator of Transcription (STAT) that transduce cytokine-mediated signals, and are associated with multiple membrane cytokine receptors such as common gamma chain (CGC) receptors and the glycoprotein 130 transmembrane proteins.[9] JAK3 and JAK1 are components of the CGC cytokine receptor complexes that are responsible for the signaling of the inflammatory cytokines interleukin (IL)-2, -4, -7, -9, -15 and -21; whereas IL-12 and IL-23 signal through JAK2 and Tyk2.[10] Propagation of these signals is important in the amplification of inflammatory responses.

Upadacitinib is a novel JAK1 inhibitor currently being developed for the treatment of adult patients with inflammatory diseases such as RA, CD, PsA, UC, AD, AxSpA, and Takayasu arteritis. In an in-vitro setting, upadacitinib potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit/risk profile in patients with GCA. Upadacitinib has reduced activity against JAK2 and JAK3 which may mitigate JAK2 inhibitory effects on erythropoiesis and myelopoiesis as well as immunosuppressive effect mediated by JAK3 inhibition.

By preferentially targeting JAK1, it is anticipated that upadacitinib will demonstrate the ability to abrogate signaling of key cytokines involved in the pathogenesis of GCA. Extensive preclinical, ex vivo, and in vivo studies have demonstrated robust inhibition of the JAK1-dependent cytokines IL-6 and Interferon gamma (IFN-γ). These two cytokines have been strongly implicated in the pathogenesis of GCA. IL-6 receptor blockade with tocilizumab has demonstrated efficacy in GCA in Phase 2 and Phase 3 studies.[4,5] However, preclinical and translational human studies have suggested that even in the setting of high dose CS with resultant reduction of IL-6 pathway, there persists a level of subclinical inflammation driven largely by IFN-γ.[11,12] Serial biopsies of patients with GCA treated with high dose CS have demonstrated that the IL-6 cytokine pathway is highly responsive to standard CS therapy, whereas the IFN-γ pathway is resistant to steroid-mediated immunosuppression.[13] Moreover, direct IFN-γ blockade abrogates STAT1 activation, reduced expression of ICAM-1, CXCL9, 10, 11 and prevents macrophage adhesion/infiltration.

Similarly, treatment with the relatively non-selective JAK inhibitor tofacitinib in a translational model of human GCA[14] demonstrated abrogation of STAT-1 signaling, reduced blood levels of IFN-γ, and prevention of T cell and macrophage accumulation in the vessel wall.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Clinically, the persistence of smoldering inflammation is supported by studies in which patients with GCA, or the closely related large vessel vasculitis Takayasu's arteritis, who were treated with the IL-6 pathway blocker tocilizumab, demonstrated persistent vasculitis of medium-sized and large vessels on autopsy despite apparent clinical response to therapy.[15,16] These data suggest that although IL-6 receptor blockade can provide reduction in flares when used continuously on the background of a forced CS taper, ultimately targeting the CS/IL-6 resistant Th1 responses will be necessary to resolve chronic smoldering vasculitis. Among those with a good response to tocilizumab in a 1-year study, over half of subjects relapsed (as early as 3 months) after discontinuation of IL-6R blockade.[17]

Using RA as a model, exposures achieved with upadacitinib 15 mg daily are anticipated to provide a level of IL-6 inhibition in range of that achieved with tocilizumab 162 mg weekly (the approved GCA dose). In addition to IL-6 blockade, there is anticipated to be robust inhibition of the IFN-γ signaling with upadacitinib. Thus, upadacitinib treatment has the potential to provide additive efficacy above and beyond that observed with IL-6R blockade alone.

Clinical Hypothesis

It is hypothesized that inhibition of cytokine signaling through the IL-6, IFN-γ, and IL-12 signaling pathways by upadacitinib, a selective JAK1 inhibitor, will result in improved ability to maintain remission with absence of GCA signs and symptoms compared to placebo (PBO), even in the setting of a more rapid reduction of CS treatment.

2.2 Benefits and Risks to Patients

Despite the observed benefit of tocilizumab over standard-of-care CS therapy (56% versus 18% rates of sustained remission from Week 12 through Week 52 defined as the absence GCA signs and symptoms, normalization of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and adherence to the CS taper regimen),[5] there is still significant room for improvement. In addition, it is not yet clear if the observed benefit translates into a potential for drug-free remission. Thus, there remains a medical need for additional therapeutic options in GCA to further increase rates of sustained remission and minimize steroid exposure.

The doses to be evaluated in Study M16-852 (upadacitinib 7.5 and 15 mg once daily [QD]) are expected to provide an optimal benefit/risk profile to support chronic administration in this study population; refer to the Selection of Doses in the Study section for additional details.

Adverse events (AEs) such as infections including herpes zoster reactivation, major adverse cardiovascular events (MACE defined as cardiovascular death, non-fatal myocardial infarctions and non-fatal strokes), thrombosis, malignancies, and hematologic AEs have been observed with JAK inhibition. Upadacitinib is a novel selective JAK1 inhibitor with the ability to decrease inflammation mediated by JAK1 signaling while having less inhibitory effect on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with less selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.

An increased risk of infections including opportunistic infections (e.g., mucosal candida infections) and herpes zoster, non-melanoma skin cancer (NMSC), and abnormal laboratory changes (e.g., elevations of

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

serum transaminases, lipids, and creatine phosphokinase; and reductions in hemoglobin and white blood cells) have been observed with upadacitinib therapy.

In ORAL Surveillance, a study of a different JAK inhibitor, tofacitinib, in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of all-cause mortality, malignancies, MACE and thrombosis (overall thrombosis, deep vein thrombosis, and pulmonary embolism) were seen in patients treated with tofacitinib versus TNF blockers.[7] These higher rates were primarily observed in patients 65 years of age and older, patients with a history of atherosclerotic cardiovascular disease, and patients with other cardiovascular risk factors (such as current or past long-time smokers). Although upadacitinib clinical trial data to date have not indicated a higher risk for MACE, venous thromboembolism, malignancies excluding NMSC, or deaths in RA patients treated with upadacitinib versus adalimumab, the findings of the ORAL Surveillance study may potentially also apply to other JAK inhibitors and an increased risk for these events compared to TNF blockers cannot be completely excluded. Therefore, the investigator should consider the benefits and risks of upadacitinib treatment and suitable treatment alternatives in determining study participation and the continued use of upadacitinib in patients 65 years of age and older, patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, patients who are current or past long-time smokers, and/or patients with other malignancy risk factors (e.g., current malignancy or history of malignancy).

The results of genetic toxicology testing indicate that upadacitinib is not genotoxic; however, upadacitinib is teratogenic based on animal studies, which necessitates avoidance of pregnancy in females of childbearing potential. Based on the calculated safety margins for human fetal exposure with seminal fluid transfer, there is judged to be no risk to the pregnancy of female partners of male subjects who are treated with upadacitinib.

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.[18]

Taken together, the safety and efficacy data from upadacitinib studies to date show a favorable benefit:risk profile for upadacitinib and support the continued investigation of upadacitinib in patients with various autoimmune/inflammatory conditions.

In view of the coronavirus disease 2019 (COVID-19 [coronavirus SARS-CoV-2]) pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Period 1

To evaluate the efficacy of upadacitinib 7.5 mg once daily (QD) and 15 mg QD in combination with a 26-week CS taper regimen compared to PBO in combination with a 52-week CS taper regimen, as measured by the proportion of subjects in sustained remission at Week 52, and to assess the safety and tolerability of upadacitinib in subjects with GCA.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Period 2

To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects who achieved remission in Period 1.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving sustained remission at Week 52. Sustained remission is defined as having achieved both of the following:

- Absence of GCA signs and symptoms from Week 12 through Week 52
- Adherence to the protocol-defined CS taper regimen.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

3.3 Secondary Endpoints

Multiplicity-controlled secondary endpoints include:

1. Proportion of subjects achieving sustained complete remission from Week 12 through Week 52. Sustained complete remission is defined as having achieved all of the following: • Absence of GCA signs and symptoms from Week 12 through Week 52; • Normalization of ESR (to < 30 mm/hr; if ESR ≥ 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52; • Normalization of hsCRP (to < 1 mg/dL without elevation [on 2 consecutive visits] to ≥ 1 mg/dL) from Week 12 through Week 52; and • Adherence to the protocol-defined CS taper regimen.
2. Cumulative CS exposure through Week 52.
3. Time to first disease flare through Week 52. Disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr (attributable to GCA) AND requiring an increase in CS dose.
4. Proportion of subjects who experience at least 1 disease flare through Week 52.
5. Proportion of subjects in complete remission at Week 52. Complete remission is defined as having achieved all of the following: • Absence of GCA signs and symptoms; • Normalization of ESR (to < 30 mm/hr); if ESR ≥ 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met. • Normalization of hsCRP to < 1 mg/dL; and • Adherence to the protocol-defined CS taper regimen.
6. Proportion of subjects in complete remission at Week 24.
7. Change from Baseline in the 36-item Short Form Quality of Life Questionnaire (SF-36) Physical Component Score (PCS) at Week 52.
8. A group of four endpoints: • Number of disease flares per subject through Week 52; • Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) at Week 52; • Assessment of Treatment Satisfaction Questionnaire for Medication (TSQM) patient global satisfaction subscale at Week 52; • Rate of CS-related AEs through Week 52

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Additional Endpoints for Period 1 are:

Proportion of subjects in complete remission at Week 12
Change from Baseline in SF-36 by visit
Change from Baseline in FACIT-Fatigue by visit
Assessment of TSQM patient global satisfaction subscale by visit
Change from Baseline in EuroQoL Five Dimensions Five Levels Questionnaire (EQ-5D-5L) by visit
Assessment of Patients' Global Impression of Change (PGIC) by visit
Change from Baseline in Patient Global Assessment (PGA) by visit
Proportion of subjects with GCA-related Health Resource Utilization by visit.
Proportion of subjects in remission at each visit through Week 52. Defined as: • Absence of GCA signs and symptoms • Adherence to the protocol-defined CS taper regimen

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Additional Endpoints for Period 2 are:

The following measures will be analyzed:

• Time to first disease flare from onset of Period 2 through Week 104. Disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr attributable to GCA AND requiring initiation of CS.
• Proportion of subjects maintaining remission from onset of Period 2 through Week 104. Remission is defined as absence of GCA signs and symptoms and CS-free.
• Cumulative CS exposure (Period 2 and inclusive of Periods 1 and 2) through Week 104

• Proportion of subjects in complete remission at Week 104. Complete remission is defined as having achieved all of the following:
  • Absence of GCA signs and symptoms;
  • Normalization of ESR (to < 30 mm/hr); if ESR ≥ 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met;
  • Normalization of hsCRP (to < 1 mg/dL); and
  • CS-free.

• Proportion of subjects who experience at least 1 disease flare from onset of Period 2 through Week 104
• Number of disease flares per subject from onset of Period 2 through Week 104
• Change in SF-36 from onset of Period 2 through Week 104
• Change in FACIT-Fatigue from onset of Period 2 through Week 104
• Assessment of TSQM patient global satisfaction subscale from onset of Period 2 through Week 104
• Change in EQ-5D-5L from onset of Period 2 by visit through Week 104
• Assessment of PGIC from onset of Period 2 through Week 104
• Proportion of subjects with GCA-related Health Resource Utilization at Week 104.

3.4 Safety Endpoints

Safety will be assessed by AE monitoring, physical examination, vital signs, electrocardiogram and clinical laboratory testing during the entire study. Laboratory assessments will include hematologic parameters, chemistry, liver function tests, and lipid parameters. A 30-Day Follow-Up visit will be done for all subjects who either terminate early from or complete the study.

3.5 Pharmacokinetic Endpoints

Blood samples to measure plasma upadacitinib and possibly other concomitant medications will be collected during Period 1 only, at the visits indicated in the Activity Schedule (Appendix D). A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values for upadacitinib oral clearance (CL/F) and apparent

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. Data from this study may be combined with data from other studies for the population pharmacokinetic analyses.

3.6 Patient Experience Endpoints

Data on patient experience will be collected by questionnaire at the Baseline visit and answers will be recorded in the electronic case report form (eCRF). The objective of the research is to obtain relevant information about patient experiences regarding the burden of GCA disease and treatment.

3.7 Biomarker Exploratory Research

Optional blood samples for exploratory research will be collected as described in the Activity Schedule (Appendix D). Prognostic and predictive biomarker signatures may be evaluated. Biomarker assessments may include nucleic acids, proteins, metabolites, or lipids. Exploratory research will focus on GCA and upadacitinib. The objective of research is to analyze samples for biomarkers that will help to understand the subject's disease and response to upadacitinib. Genes of interest may include (but not limited to) those associated pharmacokinetics (drug metabolizing enzymes, drug transport proteins), genes within the target pathway (JAK, Tyk2, tumor necrosis factor [TNF]), or other genes believed to be related GCA and other inflammatory diseases (human leukocyte antigens [HLA], IL). Research may also include epigenetic changes in DNA that may associate with the subject's response to treatment or disease. Samples for ribonucleic acid (RNA) and proteomics will be used to research if any genetic variants result in changes to gene expression or protein concentrations.

These assessments may be explored in the context of GCA or related conditions and/or upadacitinib or drugs of similar classes. Research on samples collected in Germany will be restricted to GCA and upadacitinib. The results from these analyses are exploratory in nature and may not be included with the clinical study report.

The samples may be retained for no longer than 20 years after study completion or per local requirements.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study M16-852 is a Phase 3, global, multicenter, randomized, double-blind, PBO-controlled study. Approximately 420 subjects will be enrolled into this study.

The study population will consist of adult subjects who are at least 50 years of age with a diagnosis of active GCA, either new onset or relapsing disease, within 8 weeks of Baseline. Active GCA is defined by the presence of at least one of the following: unequivocal cranial symptoms of GCA, unequivocal symptoms of PMR, or other features judged by the investigator to be consistent with GCA or PMR flares, AND an ESR ≥ 30 mm/hr or CRP ≥ 1 mg/dL.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

New onset disease is defined as diagnosis of GCA within 8 weeks of Baseline. Relapsing disease is defined as active GCA in a subject who has failed at least one attempted CS taper.

The study will allow enrollment of a minimum of 30% of subjects with new onset disease and up to 70% of subjects with relapsing disease. The study will also allow enrollment of up to 20% of subjects with previous use of an IL-6 inhibitor with discontinuation based on reasons other than disease flare.

The study duration will include a 35-day maximum Screening Period: a 52-week randomized, double-blind, parallel-group treatment period (Period 1); a 52-week blinded extension period in which subjects may either be re-randomized or continue their original treatment assignment (Period 2); and a 30-day follow-up period.

In Period 1, subjects who meet eligibility criteria will be randomized in a 2:1:1 ratio to 1 of 3 treatment groups:

- Upadacitinib 15 mg administered daily + 26-week CS taper regimen (n = 210)
- Upadacitinib 7.5 mg administered daily + 26-week CS taper regimen (n = 105)
- PBO administered daily + 52-week CS taper regimen (n = 105)

Subjects must have received treatment for active GCA at a dose of ≥ 40 mg prednisone (or equivalent) at any time prior to Baseline and must be receiving prednisone (or prednisolone) ≥ 20 mg QD at Baseline. Subjects must have GCA that, in the opinion of the investigator, is clinically stable to allow the subject to safely initiate the protocol-defined CS taper regimen.

Starting at Baseline, all subjects will switch from CS obtained outside of the study to CS provided by the sponsor with the oral prednisone or prednisolone dose at 20, 30, 40, 50, or 60 mg QD. The initial dose of prednisone or prednisolone will be at the discretion of the investigator, based on disease severity and comorbid medical conditions, but should be at a minimum of 20 mg QD at Baseline. At Baseline, if a subject is on a dose other than 20, 30, 40, 50, or 60 mg QD, the dose should be rounded up or down, as clinically indicated per investigator discretion, to the nearest of these doses. If a subject has already taken the CS dose at home on the day of the Baseline visit, dosing should not be repeated with sponsor -provided CS. Prednisone or prednisolone will be tapered according to a predefined schedule over a 26- or 52-week period. Open-label prednisone or prednisolone will be provided until the dose is tapered to 20 mg/day. Subsequently, blinded prednisone or prednisolone will be provided for the remaining blinded taper regimen through Week 52. See Section 5.8 for additional details regarding CS therapy during the study.

Subjects assigned to either dose of upadacitinib who achieve sustained remission for at least 24 consecutive weeks prior to the Week 52 Visit (at the end of Period 1) will be re-randomized in a 2:1 ratio to either continue on upadacitinib or switch to PBO in Period 2. Subjects who achieved sustained remission for at least 24 weeks prior to the Week 52 visit (at the end of Period 1) who were assigned to PBO in Period 1 will continue to receive PBO in Period 2. Remission is defined as absence of GCA signs and symptoms AND adherence to the protocol-defined CS taper regimen or CS-free.

At Week 52, subjects who have absence of GCA signs and symptoms AND are CS-free at the Week 52 visit, but do not achieve sustained remission for at least 24 consecutive weeks prior to the Week 52

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Visit, will continue in Period 2 on their originally randomized treatment assignment. All other subjects will be discontinued from study drug and the study at the end of Period 1.

Subjects who discontinue study drug during Period 1 should receive treatment at the investigator's judgment, in accordance with local standard-of-care (which could include tocilizumab), and continue to follow the regular visit schedule for the remainder of Period 1 and adhere to the Period 1 study procedures as noted in Appendix D.

In Period 2, subjects who experience a flare (defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement > 30 mm/hr attributable to GCA, AND requiring initiation of CS) will start open-label escape therapy with prednisone or prednisolone at investigator's discretion. A flare may be documented at either a scheduled or unscheduled visit. Subjects meeting flare criteria will return within approximately 4 weeks after the visit in which flare was determined for reassessment. The reassessment can occur at either a regularly scheduled or unscheduled visit. If the subject does not have absence of GCA signs and symptoms within approximately 4 weeks after the visit in which flare was determined, they will be discontinued from study drug. Subjects who discontinue study drug should receive treatment at the investigator's judgment, in accordance with local standard-of-care (which could include tocilizumab), and continue to follow the regular visit schedule for Period 2 and adhere to the study procedures as noted in Appendix D.

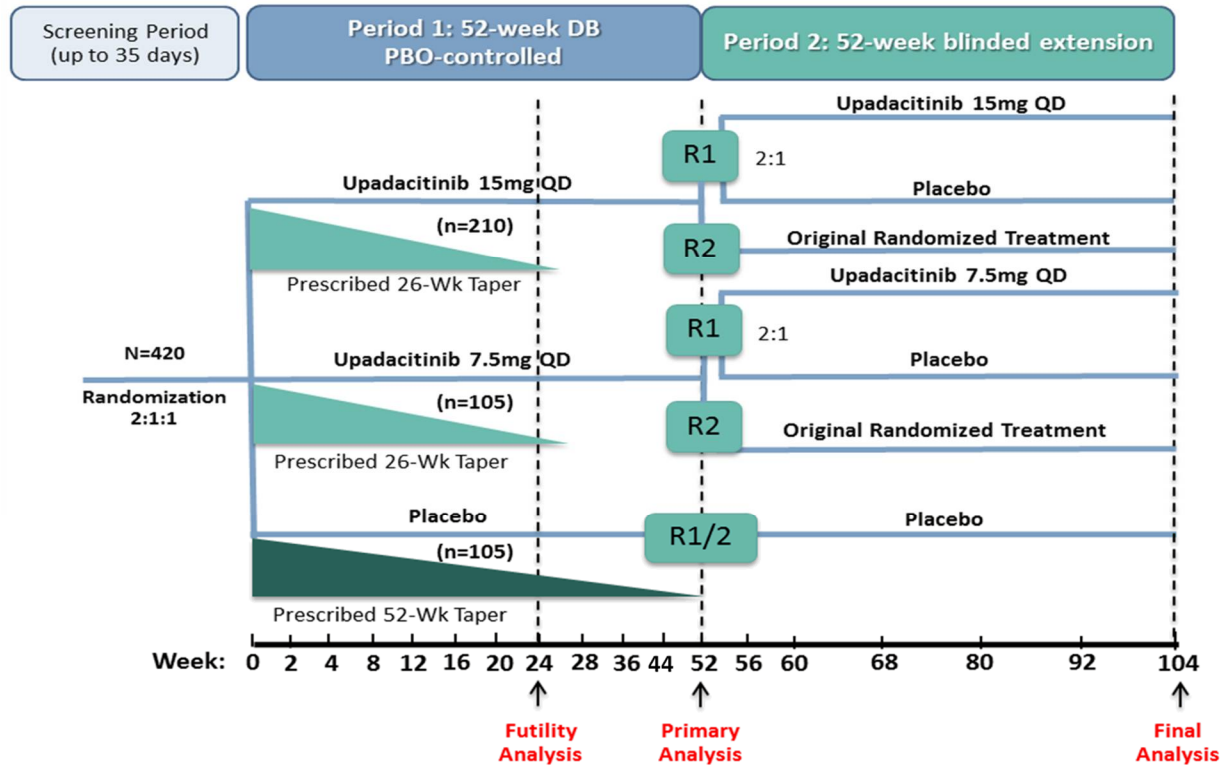
An independent, external data monitoring committee (DMC) will be established for periodic review of unblinded safety data and to ensure subject safety. In addition, a futility analysis will be conducted by the DMC to assess lack of efficacy once the first 140 enrolled subjects complete 24 weeks of treatment. Study sites and subjects will remain blinded for the duration of the study. After the last subject completes the Week 52 visit the Sponsor will be unblinded to Period 1 study drug assignment to facilitate regulatory filings. See Section 6.3 and Section 7.5 for additional details regarding the DMC and the planned futility analysis.

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

See Section 5 for information regarding eligibility criteria.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Figure 1. Study Schematic



R1 = sustained remission for 24 consecutive weeks prior to Week 52; R2 = remission at Week 52 only

4.2 Discussion of Study Design

Choice of Control Group

Placebo control will be used in this study to address potential confounding factors, such as placebo effect, potential investigator bias in safety and efficacy assessment or regression to the mean in endpoint evaluation.

The control group in this study will be placebo plus a 52-week CS taper regimen and represent a CS monotherapy taper regimen. A 52-week duration for CS taper was chosen for the control group because it is consistent with clinical practice standard of care.

Appropriateness of Measurements

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

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Suitability of Subject Population

This study will enroll adult female and male subjects who are at least of 50 years of age at the time of the Screening visit who have been diagnosed with GCA and who have active disease within 8 weeks of Baseline. The study population selected in this study reflects the standard population for GCA trials with new interventions.

Selection of Doses in the Study

This Phase 3 study will evaluate 2 doses of upadacitinib (7.5 or 15 mg QD) using the once-daily tablet formulation. The selection of doses was informed by results from the exposure-response relationships characterized in Phase 2 studies in RA (Studies M13-537 and M13-550), the Phase 3 clinical trials in RA (Studies M13-549 [SELECT-NEXT] and M13-542 [SELECT-BEYOND]), and the published results for Phase 2 and Phase 3 studies of the IL-6 inhibitor tocilizumab in GCA.[4,5]

Exposure-response analyses of the two Phase 2 studies in RA using the immediate-release formulations (doses from 3 mg twice daily [BID] to 18 mg BID and 24 mg QD) indicated that the 6 mg BID dose (equivalent to the 15-mg QD dose) approaches the plateau of efficacy in RA, and increasing the dose to 12 mg BID (equivalent to the 30-mg QD dose) appears to result in modest incremental efficacy benefit.[19,20] A bioavailability study has demonstrated that a 15 mg QD regimen of the once-daily formulation provide equivalent daily area under the curve (AUC) and comparable maximum serum concentration (C_{max}) and minimum serum concentration (C_{min}) to 6 mg BID of the immediate-release capsule formulation used in Phase 2 studies in RA under fasting conditions.[21]

Results from the first two RA Phase 3 clinical trials (Study M13-549 [SELECT-NEXT] and Study M13-542 [SELECT-BEYOND]) evaluating upadacitinib in subjects with moderate to severe RA showed that after 12 weeks of treatment, both doses of upadacitinib (15 mg and 30 mg QD) met the study's primary endpoints of ACR20 and Low Disease Activity (LDA). Key secondary endpoints were also achieved. Study M13-549 evaluated upadacitinib compared to PBO in subjects who did not adequately respond to treatment with conventional-synthetic disease-modifying antirheumatic drugs (csDMARD-IR), while Study M13-542 evaluated upadacitinib compared to PBO in subjects who did not adequately respond to treatment with biologic DMARD antirheumatic drugs (bDMARD-IR). Results from the Phase 2 and Phase 3 RA studies support the use of upadacitinib 15 mg as an efficacious dose in RA, and this dose is also expected to be efficacious in GCA.

In addition, a 7.5 mg dose will also be evaluated to ensure the minimal efficacious dose in GCA is characterized. Since GCA affects an older population with co-morbid conditions and requires initiation of high dose CS, this population is potentially at greater risk of infections. As such, a 7.5 mg dose may provide an optimal benefit/risk profile to support chronic administration in GCA patients.

The doses to be evaluated in Study M16-852 (upadacitinib 7.5 mg and 15 mg QD) are predicted to provide exposures that are lower than the no-observed-adverse-effect level (NOAEL) exposures from the preclinical toxicology studies as well as the highest exposures that were previously evaluated and found to be safe and well tolerated in healthy volunteers in Phase 1 studies and in subjects with RA or CD in Phase 2 studies. There is now extensive patient exposure to upadacitinib 15 and 30 mg QD in the ongoing Phase 3 RA program with a preliminary safety profile consistent with Phase 2 studies of upadacitinib as well as the safety profile observed with JAK inhibitors as a class. Age in adults has no impact on upadacitinib pharmacokinetics based on population pharmacokinetic analyses across Phase 1,

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

RA Phase 2, and CD Phase 2 studies. Results from hepatic and renal impairment studies of upadacitinib suggest a limited increase in upadacitinib exposure with hepatic or renal impairment. Therefore, subjects with GCA are not expected to have a clinically relevant difference in upadacitinib plasma exposures from previous observations in subjects with RA.

Efficacy in GCA was demonstrated for an IL-6 receptor inhibitor, tocilizumab, using doses that were efficacious in RA (162 mg subcutaneous [SC] injection once weekly and 162 mg SC every 2 weeks).[4,5]

Therefore, the 7.5 mg and 15 mg QD upadacitinib doses selected for Study M16-852, dosed for up to 104 weeks are expected to provide an acceptable efficacy and safety profile.

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.

Disease Activity

- 1. Diagnosis of GCA according to the following criteria:
  - Adult male or female, at least 50 years of age
  - History of ESR ≥ 50 mm/hour or high sensitivity C-reactive protein (hsCRP)/CRP ≥ 1.0 mg/dL
  - Presence of at least one of the following:
    - Unequivocal cranial symptoms of GCA (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication), or
    - Unequivocal symptoms of PMR (shoulder and/or hip girdle pain associated with inflammatory morning stiffness).
  - Presence of at least one of the following:
    - Temporal artery biopsy revealing features of GCA, or
    - Evidence of large vessel vasculitis by angiography or cross-sectional imaging (such as magnetic resonance imaging [MRI], computed tomography [CT] or positron emission tomography [PET]), assessed by a qualified radiologist experienced in evaluating large vessel vasculitis, or ultrasound of temporal arteries assessed by a qualified physician experienced in evaluating large vessel vasculitis.
- 2. Active GCA, either new onset or relapsing, within 8 weeks of Baseline. Active disease is defined by the presence of an ESR ≥ 30 mm/hr or hsCRP/CRP ≥ 1 mg/dL AND at least one of the following: unequivocal cranial symptoms of GCA, unequivocal symptoms of PMR, or other features judged by the investigator to be consistent with GCA or PMR flares.
- 3. Subjects must have received treatment with ≥ 40 mg prednisone (or equivalent) at any time prior to Baseline and be receiving prednisone (or prednisolone) ≥ 20 mg QD at Baseline.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- 4. Subjects must have GCA that, in the opinion of the investigator, is clinically stable to allow the subject to safely initiate the protocol-defined CS taper.

Contraception

- 5. Women of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing.
  Note: subjects with borderline serum pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result.
- 6. If female, subject must be either postmenopausal, OR permanently surgically sterile OR, for women of childbearing potential, practicing at least 1 protocol-specified method of birth control (Section 5.2) that is effective from Study Day 1 through at least 30 days after the last dose of study drug. Additional local requirements may apply; country-specific requirements are provided in Section 5 of the Operations Manual.
- 7. Female subjects must not be pregnant, breastfeeding, or considering becoming pregnant during the study or within 30 days after the last dose of study drug.

Consent

- 8. Subjects must be able to understand and adhere to all protocol requirements and must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.
- 9. Are willing and able to comply with procedures required in this protocol.

Laboratory Values

- 10. Laboratory values must meet the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase ≤ 2 × upper limit of normal (ULN)
  - Serum alanine transaminase ≤ 2 × ULN
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease formula ≥ 30 mL/min/1.73 m^2
  - Total white blood cell (WBC) count ≥ 2,500/µL
  - Absolute neutrophil count (ANC) ≥ 1,500/µL
  - Platelet count ≥ 100,000/µL
  - Absolute lymphocyte count (ALC) ≥ 750/µL
  - Hemoglobin ≥ 9 g/dL.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Subject History

- 11. 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 electrocardiogram (ECG) performed during Screening.
- 12. Subject must not have a history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.
- 13. Subject must have no current or past history of infection including:
  - No history of two or more episodes of herpes zoster, or one or more episodes of disseminated herpes zoster;
  - No history of one or more episodes of disseminated herpes simplex (including eczema herpeticum);
  - No human immunodeficiency virus (HIV) infection defined as confirmed positive anti-HIV antibody (HIV Ab) test;
  - Subject does not have active tuberculosis (TB) and does not meet TB exclusionary parameters (specific requirements for TB testing are provided in the operations manual);
  - ***For subjects in Japan:*** No positive result of beta-D-glucan or two consecutive indeterminate results of beta-D-glucan (screening for *Pneumocystis jirovecii* infection) during the Screening Period;
  - No active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the Baseline Visit;
  - No 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;
  - No active hepatitis B virus (HBV) or hepatitis C virus (HCV) defined as:
    - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody (HBs Ab) positive [+] subjects in Japan only);
    - HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab).
  - Confirmed active COVID-19: the Baseline Visit must be at least 14 days from the onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement of symptoms;
  - Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high-risk behavior should undergo molecular (e.g., PCR) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days following potential exposure.
- 14. Subject must not have any underlying medical disease or problems including but not limited to the following:
  - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting, and aorto-coronary bypass surgery or other ischemic events unrelated to GCA

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Uncontrolled hypertension defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
- Has been a previous recipient of an organ transplant which requires continued immunosuppression
- History of gastrointestinal perforation (other than due to appendicitis or mechanical injury), diverticulitis or have a significantly increased risk for gastrointestinal perforation per the investigator's judgment
- Conditions that could interfere with drug absorption including but not limited to short bowel syndrome
- History of any malignancy except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix.

- 15. Subject must not have undergone any major surgical procedure (except cutaneous procedures) within 60 days prior to the Baseline and must not have any planned surgery during the trial that would impact study procedures or assessments.
- 16. Subject must not be permanently wheelchair-bound or bedridden.
- 17. Subject must not have any clinically significant medical condition or any other reason which, in the opinion of the investigator, would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.

Concomitant Medications

- 18. Subject has not been treated with any investigational drug of chemical or biologic nature (see Section 5.3 for additional information on biologic therapies) within a minimum of 30 days or five half-lives (whichever is longer) prior to the first dose of study drug or is not currently enrolled in another interventional clinical study.
- 19. Subject must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from Screening through the end of the study or strong CYP3A inducers 30 days prior to study drug administration through the end of the study (refer to Table 1 in Section 5.3 for examples of commonly used strong CYP3A inhibitors and inducers).
- 20. Subject must not have received any live vaccine within 4 weeks (8 weeks for subjects in Japan) prior to the first dose of study drug, or expected to need live vaccination during study participation including at least 4 weeks (8 weeks for subjects in Japan) after the last dose of study drug.
- 21. Subject must not have had prior exposure to any JAK inhibitor (including but not limited to upadacitinib, tofacitinib, ruxolitinib, baricitinib, and filgotinib).
- 22. Subject must not have been treated with an interleukin-6 (IL-6) inhibitor (including but not limited to tocilizumab, sirukumab, and sarilumab) within 4 weeks of Baseline. Subjects previously treated with an IL-6 inhibitor must not have experienced disease flare during treatment.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- 23. Subject must not have received a biologic or non-biologic DMARD within at least five times the mean terminal elimination half-life of a drug or must follow the washout period specified below:
  - Anakinra within 1 week of Baseline;
  - Methotrexate, hydroxychloroquine, cyclosporine, azathioprine, or mycophenolate within 4 weeks of Baseline;
  - ≥ 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);
  - Cell-depleting agents (e.g., anti-CD 20) or alkylating agents including cyclophosphamide within 6 months of Baseline.
- 24. Subject must not have chronic use of systemic (oral, intravenous, and/or intramuscular) CS for > 4 years or if ≤ 4 years, an inability, in the opinion of the investigator, to withdraw from CS treatment through the protocol-defined taper regimen.
- 25. Subject must not have used oral CS for conditions other than GCA within 4 weeks of Baseline or intravenous CS within 4 weeks of Baseline. Subjects must not have had > 2 courses of systemic CS therapy to treat conditions other than GCA within 1 year prior to baseline.
- 26. Subject must not have a 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, or to corticosteroids.
- 27. Subject must not have received oral Traditional Chinese Medicines within 4 weeks prior to Baseline (refer to Section 5.3).

5.2 Contraception Recommendations

Contraception Requirements for Females

A woman who is permanently surgically sterile or postmenopausal is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Surgically sterile is defined as:

- Bilateral oophorectomy (surgical removal of both ovaries); or
- Bilateral salpingectomy (surgical removal of both fallopian tubes); or
- Hysterectomy (surgical removal of uterus).

Postmenopausal is defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle stimulating hormone (FSH) level ≥ 30 mIU/mL.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

For a woman who is ≤ 55 years of age and is not permanently surgically sterile, as defined above, and has had no menses for 12 or more months, FSH should be tested at Screening.

- If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol -specified contraception is required.
- If the FSH is tested and the result is consistent with post-menopausal status, contraception is not required.
- If the FSH is tested and the result is consistent with pre-menopausal status, contraception is required and pregnancy testing requirements for women of childbearing potential must be followed as described in the Study Activities Table (Appendix D).

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control that is effective from Study Day 1 (or earlier) through at least 30 days after the last dose of study drug:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Bilateral tubal occlusion/ligation (***For subjects in Japan:*** Bilateral tubal ligation).
- Vasectomized partner(s), provided the vasectomized partner has received medical confirmation of the surgical success and is the only sexual partner.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (for example, using calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable.

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

If during the course of the study a woman becomes surgically sterile or post-menopausal (defined above) and complete documentation is available, contraceptive measures as defined above are no longer required.

It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

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

Contraceptive counseling

At each visit, the study staff should review the pregnancy avoidance recommendations with each female of childbearing potential and document this discussion in the subject's source records.

Females for whom the childbearing potential changes during the study due to meeting any of the criteria for non-childbearing potential above do not need to continue using birth control during or following study drug treatment.

Additional local requirements may apply; refer to Section 5 of the Operations Manual for country -specific requirements. For participating countries having no additional country specific requirements, the above-mentioned contraceptive requirements should be followed in full.

5.3 Prohibited Medications and Therapy

Biologic Therapies

Subjects must have discontinued any biologic therapies with immunosuppressive potential prior to the first dose of study drug as specified in the washout procedures (Eligibility Criterion 23, Section 5.1). For all other biologic therapies, contact the AbbVie Therapeutic Area Medical Director (TA MD) for the washout period required prior to the first dose of study drug.

Biologic therapies with immunosuppressive potential are prohibited medications through the end of study drug administration, and include, but are not limited to, the following:

- Abatacept
- Adalimumab
- Anakinra
- Anifrolumab
- Belimumab
- Certolizumab
- Dupilumab
- Etanercept
- Golimumab
- Guselkumab
- Infliximab
- Ixekizumab
- Lebrikizumab
- Natalizumab

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Nemolizumab
- Rituximab
- Risankizumab
- Sarilumab
- Secukinumab
- Tocilizumab
- Tralokinumab
- Ustekinumab
- Vedolizumab

Immunosuppressants

Introduction of additional systemic immunosuppressants (such as methotrexate, hydroxychloroquine, cyclosporine, azathioprine, or mycophenolate) concurrent with study drug is prohibited from 4 weeks prior to first dose of study drug through the end of the study. Subjects who discontinue study drug may receive treatment with immunosuppressants in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

Parenteral Corticosteroids

Intra-articular, trigger-point/tender point injection, intra-bursa, or epidural administration of CS is not permitted during Period 1 of the study. Section 5.4 describes use of CS for non-GCA-related conditions that is allowed during the study. During Period 2 of the study, one intra-articular, trigger-point/tender point injection, intra-bursal injection, epidural, or intra-muscular injection is allowed for non-GCA-related conditions if it meets the permitted amount of CS allowed in Period 2 as described in Section 5.4.

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors is prohibited from Screening through the end of the study and strong CYP3A inducers are prohibited from 30 days prior to study drug administration through the end of the study. Commonly used strong CYP3A inhibitors and inducers are listed in Table 1. In addition, herbal therapies and other traditional medicines with unknown effects on CYP3A are not permitted from Screening through the end of study drug administration.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

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

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir	Apalutamide
Ceritinib	Carbamazepine
Cobicistat	Enzalutamide
Clarithromycin	Ivosidenib
Conivaptan	Lumacaftor
Grapefruit (fruit or juice)	Mitotane
Idelalisib	Phenytoin
Itraconazole	Rifampin (Rifampicin)
Ketoconazole	Rifapentine
Mibefradil	St. John's Wort
Nefazodone	Avasimibe
Nelfinavir	
Posaconazole	
Ritonavir (alone or in combination danoprevir, elvitegravir, indinavir, lopinavir, nirmatrelvir, paritaprevir, saquinavir, telaprevir, tipranavir, ombitasvir and/or dasabuvir)	
Telithromycin	
Troleandomycin	
Voriconazole	

Investigational Drugs

The use of any investigational drug within 30 days or five half-lives of the drug (whichever is longer) is prohibited. Investigational drugs are also prohibited during the study.

Vaccines

If the subject and investigator choose to administer live vaccines with replicating potential, these vaccinations must be completed (per local label) at least 4 weeks (8 weeks for subjects in Japan) before first dose of study drug. Live vaccinations with replicating potential are prohibited during the study participation including at least 30 days after the last dose of study drug.

Examples of live vaccines with replicating potential include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Herpes zoster (Zostavax®, live attenuated);
- Rotavirus;
- Varicella (chicken pox);

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Measles-mumps-rubella or measles-mumps-rubella-varicella;
- Oral polio vaccine;
- Smallpox/monkeypox vaccine capable of replicating (ACAM2000®);
- 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), pertussis (Tdap), and SARS-CoV-2 (inactivated, messenger RNA [mRNA], RNA). Whenever possible, subjects should not have received a COVID-19 vaccination in the 7 days prior to randomization or plan to receive a COVID-19 vaccination within the first 7 days after initiation of study drug. Viral vector vaccines that are not of replicating potential (such as Convidecia and Convidecia Air to treat Covid-19) are allowed.

JAK/TYK2 Inhibitors

JAK Inhibitors are prohibited during the study. Oral and topical JAK/TYK2 inhibitors (e.g., commercial upadacitinib [Rinvoq®], tofacitinib [Xeljanz®], ruxolitinib [Jakafi®; Opzelura®], baricitinib [Olumiant®], peficitinib [Smyraf®], abrocitinib [PF-04965842], and Cibinqo®], filgotinib) [Jyseleca®], fedratinib [Inrebic ®], and deucravacitinib [Sotyktu™])

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 within 30 days prior to Screening and/or receives during the study must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency must be recorded in the eCRF. Also, medications taken for GCA since date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, route of administration and reason for discontinuation, if known.

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Throughout the study, addition of a biologic or non-biologic immunomodulators other than CS while taking blinded study drug (upadacitinib or PBO) is not permitted for rescue.

Inhaled and nasal CS for stable medical conditions are allowed during the study but must have been at a stable dose for ≥ 4 weeks prior to the Baseline Visit. Short-term use (≤ 10 days) of CS (oral, inhaled, nasal, intravenous, or intramuscular) for non-GCA-related conditions for events such as exacerbation of asthma or chronic obstructive pulmonary disease, allergic reactions, or serious infection when additional CS may be required to prevent adrenal insufficiency (a total of up to 100 mg of prednisone or equivalent

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

through 52 weeks in Period 1 and a total of up to 100 mg of prednisone or equivalent through 52 weeks in Period 2) is allowed during the study.

Subjects should be treated with anti-platelet therapy (aspirin or clopidogrel) at the discretion of the investigator and in accordance with local standard-of-care practice.

Subjects should receive oral calcium and 25-hydroxy vitamin D supplementation (calcium 1200 – 1500 mg and vitamin D 800 – 1000 IU daily in divided doses), and/or bisphosphonate therapy (e.g., alendronate 70 mg weekly or zolendronate 4 mg annually), unless contraindicated, at the discretion of the investigator and in accordance with local standard-of-care practice for the prevention of glucocorticoid-induced osteoporosis. 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 [NOF]).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie TA MD or AbbVie emergency contact. Information regarding potential drug interactions with upadacitinib can be located in the upadacitinib Investigator's Brochure.

5.5 Discontinuation from Study Drug or Subject Withdrawal from Study

Subjects can request to be discontinued from participating in the study at any time for any reason including but not limited to disease progression or lack of response to treatment. The investigator may discontinue any subject's participation at any time for any reason, including but not limited to disease progression, lack of response to treatment, an AE, safety concerns, or failure to comply with the protocol.

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

- Abnormal laboratory results or AEs that either meet the criteria of discontinuation of study drug, as stated in Section 6.2 or rule out safe continuation of study drug.
- Serious infection (e.g., sepsis) that cannot be adequately controlled by anti-infective treatment or would put the subject at risk for continued participation in the trial as determined by the investigator.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus or noncardiac, non-neurologic arterial thrombosis.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion or exclusion criteria violation was noted after the subject started the study drug, when continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Any malignancy, except for a localized nonmelanoma skin cancer (NMSC) or a carcinoma in-situ of the cervix which can successfully be treated at its localization.
- The investigator determines the subject is significantly non-compliant with study procedures.
- Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injury).
- The subject experiences a serious hypersensitivity reaction without an alternative etiology.
- At Week 52, subject does not meet criteria for continuation into Period 2.

When the study drug upadacitinib or PBO are discontinued, the study drug CS dispensed by the Sponsor must also be discontinued. After discontinuation of study drug (upadacitinib or PBO and CS dispensed by Sponsor), CS will be prescribed by the investigator and dosing will be based on the investigator's judgment and in accordance with local standard of care. Medications prescribed by the investigator should be documented on the concomitant medication eCRF.

Unless subjects request to discontinue from participating in the study (withdrawal of informed consent), subjects who prematurely discontinue study drug should continue to be followed for all regularly scheduled visits for the period from which they discontinued (refer to Section 5.6).

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

AbbVie may terminate this study prematurely, either in its entirety or at any site. The 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 risk/benefit 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.

5.6 Follow-Up for Study Drug Discontinuation or Subject Withdrawal from Study

Discontinuation of Study Drug and Continuation of Study Participation

Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

If a subject prematurely discontinues study drug, the procedures outlined for the Premature Discontinuation Visit (PD 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 Visit after the last dose of study drug is required to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

resolved. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least 1 study visit at least 30 days after last dose of study drug.

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits for the period from which they discontinue as outlined in the Activity Schedule (Appendix D), unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). That is, subjects who discontinue study drug during Period 1 should continue to follow the visit schedule for the remainder of Period 1, but not continue into Period 2. Subjects who discontinue study drug during Period 2, should follow the visit schedule for the remainder of Period 2. As noted in the Activity Schedule (Appendix D), at the visits after study drug discontinuation, subjects should adhere to all study procedures except for dispensing study drug or reviewing returns and accountability, dispensing/reviewing study drug instructions, dosing diaries, pharmacokinetic sample collection, and sample collection for exploratory research. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (discontinuation of study drug treatment and study participation; withdrawal of informed consent) for any reason at any time. If a subject prematurely discontinues study drug treatment and study participation (withdrawal of informed consent) simultaneously, the procedures outlined for the PD Visit should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy.

If a subject discontinues from study (withdrawal of informed consent) following a previous discontinuation of study drug that resulted in an initial PD Visit, a second PD Visit is not required.

If a subject is discontinuing at Week 52 because they do not meet the criteria to enter Period 2, a separate PD Visit is not needed; instead, the Week 52 Visit should be performed. In addition, a 30-day Follow-Up Visit after the last dose of study drug should occur to ensure all treatment emergent AEs/SAEs have been resolved. This visit may be a telephone call if a site visit is not possible.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status, including the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. 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.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

5.7 Assessment of Disease Activity

Assessment of GCA Signs and Symptoms

Clinical signs and symptoms of GCA will be evaluated at every study visit according to the schedule of assessment and entered into the eCRF. GCA signs and symptoms include the following:

- Fever (> 38°C or 100.4°F)
- Symptoms of PMR (morning stiffness and/or pain, in the shoulder and/or hip girdles)
- Localized headache, temporal artery or scalp tenderness
- Visual signs or symptoms such as acute or subacute vision loss due to arteritic anterior ischemic optic neuropathy, transient blurry vision (generally monocular or at least affecting one eye at a time, but potentially affecting both eyes)
- Jaw or mouth pain
- New or worsened extremity claudication
- Other features judged by the Clinical Assessor to be consistent with a GCA or PMR flare.

Acute Phase Reactants: High Sensitivity C-Reactive Protein (hsCRP) and Erythrocyte Sedimentation Rate (ESR)

Knowledge of the laboratory results for hsCRP may result in inadvertent unblinding of a subject's treatment. Therefore, after the Baseline Visit, hsCRP results (analyzed and reported by the central laboratory) will not be made available to the Sponsor, the investigator, study site personnel, or the subject through the duration of the study. The Sponsor will be blinded to the hsCRP results until the time of the primary analysis.

After the Screening visit, ESR results (analyzed and reported by the local laboratory) will not be made available to the Sponsor, the investigator, the subject, and study site personnel, with the exception of the local Laboratory Assessor to prevent biased efficacy assessment. A local Laboratory Assessor will be assigned at each study site to review ESR results. Only the Laboratory Assessor is permitted to review ESR results and will advise the investigator of any ESR measurement $\geq$ 30 mm/hr.

5.8 Study Drug

Study drug includes the investigational product (IP) of upadacitinib and matching upadacitinib PBO as well as CS therapy (open label or blinded prednisone/prednisolone and matching CS PBO) included as part of the protocol-defined CS taper.

Study drug will be taken orally once daily beginning on Day 1 (Baseline) and should be taken at approximately the same time each day, with or without food. 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.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

AbbVie will supply upadacitinib, matching upadacitinib PBO, as well as open-label and blinded CS therapy (prednisone or prednisolone) and matching CS PBO included as part of the protocol-defined CS taper.

All study drug (IP and CS) must be stored at controlled room temperature (15° to 25°C/59° to 77°F). US sourced prednisone 20 mg will need to be stored protected from light and moisture. Study drug will be packaged in quantities sufficient to accommodate study design.

In cases of state of emergency or pandemic situations, study drug shipment can be made from the study site to the subject if allowed by local regulations. Refer to the Operations Manual in Appendix G for details on direct-to-patient (DTP) shipment of study drug.

Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

Individual study drug information is presented in Table 2.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Table 2. Identity of Study Drug

	Investigational Product (IP)	IP	IP Placebo (PBO)	Corticosteroid (CS)	CS	CS PBO
Name	upadacitinib	upadacitinib	Matching upadacitinib PBO	Prednisone/ Prednisolone	Prednisone/ Prednisolone	Matching CS PBO
Blinded or Open Label	Blinded	Blinded	Blinded	Open Label (doses ≥ 20 mg)	Blinded (doses < 20 mg)	Blinded
Mode of Administration	Oral	Oral	Oral	Oral	Oral	Oral
Strength	15 mg	7.5 mg	N/A	1,[a] 5, 10 and 20 mg	1, 2, 5 and 10 mg	N/A
Dosing Regimen	1 upadacitinib 15 mg tablet	1 upadacitinib 7.5 mg tablet	1 upadacitinib matching PBO tablet	Per Tapering Schedule[b]	Per Tapering Schedule[a]	
Dosage Form	Tablet	Tablet	Tablet	Tablets/ Capsules	Capsules	
Frequency of administration	QD	QD	QD	QD	QD	

a. The 1-mg prednisone/prednisolone open-label dose is not needed for protocol-defined open-label taper, but may be used for escape therapy, if needed (Corticosteroid Escape Therapy during the Study).

b. The CS tapering schedule is provided in Appendix E.

Corticosteroid Therapy as Study Drug

There are two phases to the CS (prednisone or prednisolone) taper regimen:

- Open-label taper, for CS dosages from 60 mg/day to 20 mg/day
- Blinded taper, for CS dosages < 20 mg/day.

Starting at Baseline, all subjects will switch from CS obtained outside of the study to open-label oral prednisone or prednisolone provided by the Sponsor at a dose of 20, 30, 40, 50, or 60 mg QD. The initial dose of prednisone or prednisolone will be at the discretion of the investigator, based on disease severity and comorbid medical conditions, but should be at a minimum of 20 mg QD at Baseline. At Baseline, if a subject is on a dose other than 20, 30, 40, 50, or 60 mg QD, the dose should be rounded up or down, as clinically indicated per investigator discretion, to the nearest of these doses. Subjects will follow the CS Tapering Schedule as per Appendix E, completing the open-label phase and transitioning to the blinded phase of tapering depending on the CS dose at baseline (i.e., subjects starting on 20 mg/day will transition to the double-blind phase of tapering more quickly than patients starting on 60 mg/day).

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Open-label prednisone or prednisolone will be provided until the dose is tapered to less than 20 mg/day. Subsequently, blinded CS therapy and/or matching CS PBO will be provided for the remaining blinded taper regimen. While receiving blinded CS therapy, subjects will receive 1 carton containing 3 bottles of CS study drug per week and will be instructed to take 1 capsule per bottle per day; the 3 capsules combined will be equivalent to the weekly dose according to the CS Tapering Schedule (Appendix E).

Corticosteroid Escape Therapy during the Study

Subjects who require CS escape therapy for their GCA disease will be deemed non-responders in the primary analysis. Any use of CS for escape therapy throughout the study will be documented in the eCRF.

Period 1:

At every visit, an assessment of subject's disease will be made to assess if the subject can adhere to the CS tapering schedule. If subject has no flare of GCA and is able to follow the CS tapering schedule, the subject will continue receiving protocol-defined blinded or open label CS therapy in the study.

In Period 1, disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr (attributable to GCA), AND requiring an increase in CS dose.

Subjects who experience disease flare or are unable to adhere to the protocol-defined CS tapering regimen during open-label tapering of prednisone (at doses of 60 mg/day to 20 mg/day) should stop the protocol-defined CS taper and receive open-label escape therapy with prednisone or prednisolone at the discretion of the investigator. Ongoing CS use and subsequent tapering will be at the discretion of the investigator. While on open-label CS escape therapy, the subject should continue in the study for the full 52 weeks and receive blinded study drug (upadacitinib or PBO). If, after 2 weeks of open-label CS escape therapy, the investigator believes it is medically necessary to treat the subject with other available treatments, blinded study drug (upadacitinib or PBO) and CS should be discontinued and the subject should be managed based on standard-of-care therapies, which may include tocilizumab. After discontinuation of study drug (upadacitinib or PBO and CS dispensed by Sponsor), CS will be prescribed by the investigator and dosing will be based on the investigator's judgment and in accordance with local standard of care. Medications prescribed by the investigator should be documented on the concomitant medication eCRF. Subjects who are discontinued from study drug during Period 1 should continue to follow the visit schedule for the remainder of Period 1 (Section 5.6).

Subjects who experience disease flare or are unable to adhere to the protocol-defined CS tapering regimen during the blinded protocol-defined CS taper should stop the protocol-defined CS taper and receive open-label escape therapy with prednisone or prednisolone starting with at least 20 mg/day at the discretion of the investigator. Ongoing CS use and subsequent tapering will be at the discretion of the investigator. While on open-label CS escape therapy, the subject should continue in the study for the full 52 weeks and receive blinded study drug (upadacitinib or PBO). If, after 2 weeks of open-label CS escape therapy, the investigator believes it is medically necessary to treat the subject with other available treatments, blinded study drug (upadacitinib or PBO) and CS should be discontinued and the subject should be managed based on standard-of-care therapies, which may include tocilizumab. After discontinuation of study drug (upadacitinib or PBO and CS dispensed by Sponsor), CS will be prescribed

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

by the investigator and dosing will be based on the investigator's judgment and in accordance with local standard of care. Medications prescribed by the investigator should be documented on the concomitant medication eCRF. Subjects who are discontinued from study drug during Period 1 should continue to follow the visit schedule for the remainder of Period 1 (Section 5.6).

Subjects who receive CS escape therapy will be eligible to continue in Period 2 if meeting criteria for study continuation outlined in Section 4.1.

Period 2

In Period 2, disease flare is defined as an event determined by the investigator to represent recurrence of GCA signs or symptoms or an ESR measurement ≥ 30 mm/hr, AND requiring initiation of CS. Subjects who experience disease flare in Period 2 (blinded extension phase) should receive an escape regimen of open-label prednisone or prednisolone at investigator's discretion. Thereafter, open-label escape CS taper will be based on the investigator's judgment and in accordance with local standard-of-care. At the investigator's discretion, these subjects may also discontinue study drug (upadacitinib or PBO and CS dispensed by Sponsor) and receive treatment in accordance with local standard-of-care, which may include tocilizumab, and should continue to follow the visit schedule for the remainder of Period 2 (Section 5.6). After discontinuation of study drug (upadacitinib or PBO and CS dispensed by Sponsor), CS will be prescribed by the investigator and dosing will be based on the investigator's judgment and in accordance with local standard of care. Medications prescribed by the investigator should be documented on the concomitant medication eCRF.

5.9 Randomization/Drug Assignment and Blinding

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. Subjects may only be rescreened one time without prior AbbVie approval. For additional re-screening, AbbVie TA MD approval is required.

All screening activities must be completed and reviewed prior to enrollment. Subjects who meet the eligibility criteria will proceed to enrollment via the IRT system on Day 1 (Baseline Visit of Treatment Period 1). The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. A subject number is assigned at screening via IRT. Enrolled subjects will keep their screening number as their subject number throughout the study.

This study is designed to enroll 420 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Subjects in screening will be permitted to enroll even if the target number of subjects has been enrolled.

Randomization of all subjects, except for those in Japan, will be stratified by baseline CS dose (prednisone or prednisolone > 30 mg or ≤ 30 mg), prior use of an IL-6 inhibitor, and whether entering the study with new onset or relapsing disease. In Japan, the study will attempt to include a minimum of 8 subjects; no stratification will be utilized for randomization, however, data on all 3 stratification factors will be collected. In Period 1, subjects will be randomized in a 2:1:1 ratio (upadacitinib 15 mg +

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

26-week CS taper regimen, upadacitinib 7.5 mg + 26-week CS taper regimen, or PBO + 52-week CS taper regimen).

In Period 2, subjects from the Period 1 upadacitinib group who achieve remission for at least 24 weeks prior to the Week 52 visit (at the end of Period 1) will be re-randomized to either continue on upadacitinib or switch to PBO (Section 4.1); re-randomization will be stratified by baseline disease status (new onset or relapsing disease). Subjects from the Period 1 Placebo group who achieve remission for at least 24 weeks prior to the Week 52 visit (at the end of Period 1) will continue to receive PBO. In Period 2, subjects previously on upadacitinib will be re-randomized in a 2:1 ratio (upadacitinib [same dose as Period 1] or PBO). Subjects who were assigned to PBO in Period 1 will continue to receive PBO. At Week 52, subjects who have absence of GCA signs and symptoms AND are CS-free, but do not meet the above remission criteria will continue in Period 2 on their originally randomized treatment assignment. All other subjects will be discontinued from study drug at the end of Period 1.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment until the last subject completes the Week 52 visit. After the last subject completes the Week 52 visit the Sponsor will be unblinded to Period 1 and Period 2 study drug assignments to facilitate regulatory filings. The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, upadacitinib tablets and matching PBO tablets as well as CS capsules and matching PBO capsules 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 situation 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 Unblind Subject 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 (support@endpointclinical.com). For country-specific phone numbers, please see the following website: (http://www.endpointclinical.com/help-desk/).

In the event that the blind is broken before notification to the AbbVie TA MD, we request that the AbbVie TA MD 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. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable) and AbbVie. In Japan, the investigator will record all protocol deviations in the appropriate medical records at the site.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Product Complaint

A product complaint is any complaint related to the drug component of the product.

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, or packaging issues.

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

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

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

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

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

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

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

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

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

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 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 Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines.

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

Adverse Events of Special Interest

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

- Serious infections
- Opportunistic infections
- Herpes Zoster
- Active TB
- Malignancy (all types)
- Adjudicated Gastrointestinal Perforations
- Adjudicated MACE
- Anemia
- Neutropenia
- Lymphopenia
- Renal dysfunction
- Hepatic disorder
- Elevated CPK
- Adjudicated Embolic and thrombotic events (non-cardiac, non-central nervous system [CNS])

In addition to the AESIs listed above, the following adverse events will also be monitored during the study: Bone Fracture; Retinal detachment.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Adverse Event Severity and Relationship to Study Drug

Investigators will rate the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc.

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

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Severe (Grade 3 – 5)	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

The investigator will assess the relationship of the AE to the study drugs upadacitinib (or matching placebo) and prednisone/prednisolone (or matching placebo). Summary of CS-related AEs will be based on this assessment.

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

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the SAE.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. If a pregnancy occurs in a study subject information regarding the pregnancy and the outcome will be collected.

Subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration for female subjects. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

Subjects who become pregnant during the study must be discontinued (Section 5.5).

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 of the site becoming aware of the event.

6.2 Toxicity Management

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

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

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

Herpes Zoster: If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

Gastrointestinal Perforation: Subjects presenting with the onset of signs or symptoms of a gastrointestinal perforation should be evaluated promptly for early diagnosis and treatment. If the diagnosis of gastrointestinal perforation (other than due to appendicitis or mechanical injury) is confirmed, the subject must be permanently discontinued from study drug.

Major Cardiovascular Event: For subjects who develop a major cardiovascular event (MACE: acute myocardial infarction, cerebrovascular accident [stroke]) while on study drug, the investigator should

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

evaluate the benefit/risk of, and discuss with the TA MD whether it is appropriate to continue study drug.

Malignancy: Subjects who develop malignancy other than NMSC or carcinoma in situ of the cervix must be permanently discontinued from study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at an increased risk for skin cancer. Subjects who develop malignancies should be referred to appropriate specialists and managed as per standard of care.

Muscle-related symptoms: If a subject experiences symptoms suggestive of myositis or rhabdomyolysis, consider checking CPK and aldolase with clinical management and/or study drug interruption as deemed appropriate by the investigator.

Thrombosis Events: Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolus or noncardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug, OR a confirmed absolute QT interval corrected for heart rate using Fridericia's formula (QTcF) value > 500 msec.

COVID-19: Study drug should be interrupted in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects who show signs and/or symptoms with suspicion of COVID-19. Study drug may be restarted once the infection has resolved, or 5 days have passed since the COVID-19 positive test result (whichever comes last). The COVID-19 eCRF must be completed.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 3, and may require a supplemental eCRF to be completed. 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 per Table 3, the repeat testing must occur as soon as possible.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline for Upadacitinib and Matching Placebo

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

Absolute neutrophil count (ANC)	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to ≥ 1000/µL. • For confirmed < 500/µL, if value returns to ≥ 1000/µL, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
Absolute lymphocyte counts (ALC)	If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to ≥ 500/µL.
Total white blood cell count	If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to ≥ 2000/µL.
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 baseline value.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Laboratory Parameter	Toxicity Management Guideline for Upadacitinib and Matching Placebo

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	Interrupt study drug if any of the following scenarios are confirmed by repeat testing of AST/ALT:
	• ALT or AST > 3 × ULN 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.
	  • If a creatine phosphokinase (CPK) value is not available, a CPK should be drawn to exclude AST/ALT elevations related to muscle injury
	• ALT or AST > 3 × ULN along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or new-onset eosinophilia.
	• ALT or AST > 5 × ULN for more than 2 weeks.
	If ALT or AST > 8 × ULN, interrupt study drug immediately, repeat testing with a new sample, and if repeat test confirms result contact the TA MD.
	• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within 1 week (based on initial elevated value):
	  • ALT > 5 × ULN OR
	  • ALT or AST > 3 × ULN if an alternative cause is not readily identified.
	  • 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). Within 1 week of the first episode of a positive HBV DNA PCR test, a hepatologist consultation should occur 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. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason rechallenge is expected to be safe. Study drug should be discontinued if no alternative etiology can be found and ALT or AST elevations persist.
	For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

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

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Laboratory Parameter	Toxicity Management Guideline for Upadacitinib and Matching Placebo
Creatine Phosphokinase	Investigators should complete the supplemental elevated CPK eCRF for the below CPK elevation scenarios or if CPK increase is considered to be an AE by the investigator. • If a subject experiences any symptoms suggestive of myositis or rhabdomyolysis, blood for measuring CPK and aldolase levels should be drawn with clinical management as deemed appropriate by the investigator. • If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subject may continue study drug at the investigator's discretion after evaluation. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie medical monitor.

Urgent and Emergency Surgeries

For urgent and emergency surgeries the following rules will apply:

- If the subject must undergo an urgent or emergency surgery, the study drug should be interrupted at least 1 week prior to a planned urgent surgery if possible, or at the time of an emergency 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.
- Elective surgery, and interruption of study drug for such a surgery, should be avoided until after the Week 52 visit has been completed. If elective surgery is considered prior to the primary endpoint visit, it must be discussed with the TA MD and performed with TA MD approval. If the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned 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.

6.3 Data Monitoring Committee

An independent, external DMC will be established for periodic review of unblinded safety data and to alert AbbVie to possible safety concerns related to the conduct of the study to ensure subject safety. The DMC will review safety data of the first 80 enrolled subjects through 8 weeks of treatment to determine if there are any significant safety concerns that would warrant any study action. Thereafter, the DMC will review safety data on a regular basis and as needed based on the accumulating safety data and will provide recommendations to AbbVie.

The DMC Charter will describe the roles and responsibilities of the DMC members, frequency of data reviews, and relevant data to be assessed. Communications from the DMC to the Study Team will not contain information that could potentially unblind the team to subject treatment assignments.

In addition, the DMC will conduct a futility analysis as described in Section 7.5.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

6.4 Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular AEs in a blinded manner as defined by the Cardiovascular Adjudication Committee charter.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

An unblinded analysis for Period 1 will be conducted after all subjects have completed Week 52 or have prematurely discontinued the study prior to Week 52. An unblinded analysis for Period 2 will be conducted after all subjects have completed Week 104 or have prematurely discontinued the study prior to Week 104. Additional unblinded analysis in Period 2 may be conducted for regulatory purposes. To maintain integrity of the trial and avoid introduction of bias, study sites and subjects will remain blinded until all subjects have completed Period 2 (Week 104).

Statistical analyses will be described and fully documented in the Statistical Analysis Plan (SAP). The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) will be defined for Period 1 and Period 2. The FAS population in Period 1 (FAS1) includes all randomized subjects who received at least 1 dose of study drug in Period 1. The FAS population in Period 2 (FAS2) is defined as all subjects who achieved remission for at least 24 consecutive weeks prior to the Week 52 Visit (at the end of Period 1) and received at least 1 dose of study drug in Period 2. In addition, an exploratory analysis set will be defined for Period 2 to include all subjects who did not meet these remission criteria (i.e., achieve remission for at least 24 weeks prior to the Week 52 Visit) but continued in Period 2 on their originally randomized treatment assignment. Primary efficacy analysis for primary and key secondary endpoints will be carried out on the FAS1 population in Period 1 and on the FAS2 population in Period 2. Exploratory efficacy analyses for Period 2 will be conducted for selected variables for the exploratory analysis set. Subjects will be grouped according to treatment as randomized.

The Per-Protocol Analysis Set will be defined to represent a subset of the FAS1 subjects without any major protocol violations during the study which are expected to impact the primary endpoint. Subjects to be excluded from the Per-Protocol Population will be identified before the Week 52 database lock. The Per-Protocol Population will be used to analyze the primary efficacy endpoint in a sensitivity analysis. Additional analyses may be conducted on the Per-Protocol Analysis Set in order to evaluate the impact of major protocol violations.

The Safety Analysis Set will be defined for Period 1 and Period 2. The Safety Analysis Set in Period 1 will consist of all subjects who received at least 1 dose of study drug in Period 1. The Safety Analysis Set in Period 2 will consist of all subjects who received at least 1 dose of study drug in Period 2. For the Safety

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the randomized treatment.

7.3 Statistical Analyses for Efficacy

Analysis of Primary and Key Secondary Endpoints in Period 1

For the global analysis, the overall type I error rate of the primary and ranked key secondary endpoints for the 2 upadacitinib doses will be strongly controlled using a graphical multiple testing procedure.

Specifically, the testing will utilize the endpoint sequence of primary endpoint followed by key secondary endpoints in the order as specified in Section 3.2 and Section 3.3. The testing will start with the primary endpoint of 15 mg QD with $\alpha = 0.05$. Continued testing will follow a pre-specified α transfer path, which includes downstream transfer along the endpoint sequence within each dose as well as cross-dose transfer. The testing of 7.5 mg QD dose will start with transferred α if endpoint 7 in Section 3.3 of the 15 mg QD dose is significant. The group of endpoints labeled as 8 in Section 3.3 will be tested using the Hochberg procedure, conditional on significance of higher ranked endpoints. More details of the graphical procedure will be specified in the SAP. An alternative testing procedure will be done for the regulatory purposes in Japan. More details of the graphical procedure will be specified in the SAP. Unless otherwise specified, all statistical tests will be performed at a 2-sided significance level of 0.05.

The primary analysis will be conducted after all subjects have completed the Week 52 visit or have prematurely discontinued from the study prior to Week 52. For the primary efficacy endpoint, the upadacitinib groups will be compared with the PBO group using the Cochran-Mantel-Haenszel method adjusting for stratification factors. The primary approach for handling missing data will be Non-Responder Imputation incorporating multiple imputation (NRI-MI). Subjects with missing data will be counted as non-responders, except when missing at random can be reasonably assumed, which will be handled by multiple imputation. For example, missing due to COVID-19 logistical restriction or due to political conflict will be handled by multiple imputation. A sensitivity analysis will be performed based on As Observed analysis in which subjects with missing components of sustained remission at Week 52 will be excluded from analysis. Other key binary endpoints will be analyzed similarly.

For continuous change from baseline endpoints such as change from baseline in SF-36, PGA, EQ-5D-5L and FACIT-Fatigue, comparisons between the upadacitinib treatment groups and the PBO group will be carried out using the Mixed-Effect Model Repeat Measurement (MMRM) model with treatment group, visit, treatment-by-visit interaction, and stratification factors as the fixed factors and the corresponding baseline values as the covariates. TSQM, PGIC value will be analyzed using an MMRM model with treatment group, visit, treatment-by-visit interaction and stratification factors as the fixed factors. For cumulative CS dose, comparisons between the upadacitinib treatment group and the PBO group will be analyzed using a van Elteren test stratified by stratification factors. The median total cumulative prednisone dose over the 52 weeks for each treatment group and the corresponding 95% CI for the median will be presented.

For time-to-event endpoints, median time-to-event will be reported for each treatment group. Comparisons between the upadacitinib group and the PBO group will be conducted using stratified log

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

rank test; additional analyses may be conducted using Cox's regression to include baseline values and stratification factors as covariates.

For count endpoints, comparisons between the upadacitinib treatment group and the PBO group will be carried out using Poisson regression model with treatment group and stratification factors as covariates, adjusting for exposure duration.

Other Efficacy Variables

Additional efficacy variables are listed in Section 3.3 and will be summarized for Period 1 and 2. For all the additional efficacy variables in Period 1, the summary statistics and the statistical method will be the same as the corresponding variables described in the primary and key secondary analyses. For all the additional efficacy variables in Period 2, descriptive statistics will be provided for each treatment group sequence. For binary endpoints, frequencies and percentage with 95% CI using normal approximation will be reported for each treatment group and 95% CI will be reported for treatment difference. For continuous endpoints, the mean, standard deviation, 95% CI, median, and range will be reported for each treatment group and 95% CI will be reported for treatment difference. For time-to-event endpoints, median time-to-event will be reported for each treatment group. For count endpoints, the exposure duration adjusted event rates will be reported for each treatment group.

Sample Size Estimation

The planned total sample size of 420 subjects with a 2:1:1 ratio (upadacitinib 15 mg QD: upadacitinib 7.5 mg QD: PBO QD) was determined to have at least 90% power to detect a 20% difference in sustained remission rate at Week 52 between the upadacitinib 15 mg arm and the PBO arm (assuming a response rate of 40% in the PBO arm), using Fisher's exact test, with an overall two-sided alpha = 0.05.

7.4 Statistical Analyses for Safety

Safety analyses for Period 1 and Period 2 alone and long-term safety analyses for Period 1 and Period 2 combined will be carried out using the Safety Analysis Set in Period 1 (for safety analyses for Period 1 alone and Periods 1 and 2 combined) as well as the Safety Analysis Set in Period 2 (for safety analyses for Period 2 alone) respectively, and will be based on treatments actually received regardless of the randomly assigned treatment.

Safety will be assessed by treatment-emergent adverse events (TEAEs), physical examination, laboratory assessments, ECG, and vital sign results. The number and percentage of subjects experiencing TEAEs by treatment group will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). In addition, summaries of SAEs and TEAEs by severity and relationship to study drug as assessed by the investigator will be provided. SAEs, severe TEAEs, and TEAEs that lead to premature study discontinuation will be listed. Changes in vital signs, physical examination results, and clinical laboratory variables at each visit as compared to baseline will be summarized. Shift of laboratory values from baseline to defined time points will be tabulated.

Missing safety data will not be imputed.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

7.5 Interim Analysis

In addition to periodic review of safety data (Section 6.3), the DMC will conduct a futility analysis to assess lack of efficacy once the first 140 enrolled subjects complete 24 weeks of treatment (approximately 70 subjects in the 15-mg active treatment arm; 35 subjects in the 7.5-mg active treatment arm and 35 in the PBO arm). A futility recommendation will be made when the futility criterion is met. Further details will be provided in the DMC Charter.

8 ETHICS

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

The protocol, informed consent form(s), recruitment materials, and all participant 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 participant 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, 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 cases of state of emergency or pandemic situations leading to difficulties in performing protocol -specified procedures, AbbVie will 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. Refer to the Operations Manual for additional details. 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 subjects against any 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.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

Electronic case report forms (eCRFs) must be completed for each subject screened and/or enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF data for this study are being collected with an electronic data capture (EDC) system called Rave®. All data entered into the eCRF will be recorded by investigative site personnel in the EDC system and will be supported by source documentation.

The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data.

In cases of state of emergency or pandemic situations, remote data review and verification 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.

Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes.

11 COMPLETION OF THE STUDY

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

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

12 REFERENCES

1. Alba MA, Garcia-Martinez A, Prieto-Gonzalez S, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine (Baltimore). 2014;93(5):194-201.
2. Proven A, Gabriel SE, Orces C, et al. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703-8.
3. Unizony S, Arias-Urdaneta L, Miloslavsky E, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res (Hoboken). 2012;64(11):1720-9.
4. Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, PBO-controlled trial. Lancet. 2016;387(10031):1921-7.
5. Stone JH, Tuckwell K, Dimonaco S, et al. Efficacy and safety of tocilizumab in patients with giant cell arteritis: primary and secondary outcomes from a phase 3, randomized, double-blind, placebo-controlled trial [abstract]. Arthritis Rheumatol. 2016;68 (Suppl 10).
6. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013;368(2):161-70.
7. Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci. 2004;117 (Pt 8):1281-3.
8. Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology, and treatment. Autoimmun Rev. 2012;11(6-7):A544-54.
9. Murray PJ. The JAK-STAT signaling pathway: input and output integration. J Immunol. 2007;178(5):2623-9.
10. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev. 2009;228(1):273-87.
11. Deng J, Younge BR, Olshen RA, et al. Th17 and Th1 T-cell responses in giant cell arteritis. Circulation. 2010;121(7):906-15.
12. Weyand CM, Younge BR, Goronzy JJ. IFN-gamma and IL-17: the two faces of T-cell pathology in giant cell arteritis. Curr Opin Rheumatol. 2011;23(1):43-9.
13. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol. 2013;9(12):731-40.
14. Zhang H, Watanabe R, Berry GJ, et al. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. Circulation. 2017. [Epub ahead of print].
15. Unizony S, Arias-Urdaneta L, Miloslavsky E, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. Arthritis Care Res. 2012;64(11):1720-9.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

16. Xenitidis T, Horger M, Zeh G, et al. Sustained inflammation of the aortic wall despite tocilizumab treatment in two cases of Takayasu arteritis. Rheumatology (Oxford). 2013;52(9):1729-31.
17. Adler S, Reichenbach S, Kuchen S, et al. Termination of tocilizumab treatment in giant cell arteritis: follow-up of patients after the RCT. Arthritis Rheumatol. 2016;68 (Suppl 10).
18. AbbVie. Upadacitinib Investigator's Brochure Edition 12. 16 August 2021.
19. Kremer JM, Emery P, Camp HS, et al. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. Arthritis Rheumatol. 2016;68(12):2867-77.
20. Genovese MC, Smolen JS, Weinblatt ME, et al. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Rheumatol. 2016;68(12):2857-66.
21. Mohamed ME, Zeng J, Song IH, et al. Pharmacokinetics of ABT-494 with the once-daily extended-release tablet formulation being utilized in the ongoing rheumatoid arthritis phase 3 trials [abstract]. Arthritis Rheumatol. 2016;68 (Suppl 10).

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	antibody
AD	atopic dermatitis
ADL	activities of daily living
AE	adverse event
ALC	absolute lymphocyte counts
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AxSpA	axial spondyloarthritis
bDMARD	biologic disease modifying antirheumatic drugs
BID	twice daily
CD	Crohn's disease
CGC	common gamma chain
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CL/F	oral clearance
CNS	central nervous system
COVID-19	coronavirus disease – 2019 (coronavirus SARS-CoV-2)
CPK	creatine phosphokinase
CRP	C-reactive protein
CS	corticosteroid(s)
csDMARD-IR	conventional-synthetic disease modifying antirheumatic drugs
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest x-ray
CYP3A	cytochrome P450 3A
DMARD	disease modifying antirheumatic drugs
DMC	data monitoring committee
DTP	direct-to-patient

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
EQ-5D-5L	EuroQol Five Dimensions Five Levels Questionnaire
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCA	giant cell arteritis
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBc Ab	hepatitis B core antibody
HBs Ab	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
hsCRP	high sensitivity C-reactive protein
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon-gamma
IL	interleukin
IL-6	interleukin-6
IMP	Investigational Medicinal Product
INR	international normalized ratio
IP	investigational product
IR	inadequate response
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus kinase
JAK1	Janus kinase 1

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

LDA	low disease activity
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MMRM	mixed-effect model repeat measurement
NK	natural killer (cells)
NMSC	non-melanoma skin cancer
NOAEL	no-observed-adverse-effect level
NOF	National Osteoporosis Foundation
NRI	non-responder imputation
PBO	placebo
PCR	polymerase chain reaction
PCS	Physical Component Score
PD	Premature Discontinuation
PD Visit	Premature Discontinuation Visit
PET	positron emission tomography
PGA	Patient Global Assessment
PGIC	Patients' Global Impression of Change
PK	pharmacokinetic(s)
PMR	polymyalgia rheumatica
PPD	purified protein derivative
PsA	psoriatic arthritis
PT	preferred term
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short Form 36
SOC	system organ class
STAT	Signal Transducer and Activator of Transcription

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TA MD	Therapeutic Area Medical Director
TEAE	Treatment-emergent adverse event
TNF	tumor necrosis factor
TSQM	Treatment Satisfaction Questionnaire for Medication
Tyk2	tyrosine kinase 2
UC	ulcerative colitis
ULN	upper limit of normal
V/F	apparent volume of distribution
WBC	white blood cell

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-852: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA

Protocol Date: 31 May 2023

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

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Immunology Development
		Statistics
		Statistics

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across Period 1 and Period 2; the individual activities are described in detail in the **Operations Manual**. Allowed modifications due to a state of emergency or pandemic situation are detailed within the Operations Manual.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

abbvie

Study Activities Table

Activity	Period 1													Period 2								PD	FU
	Screening	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 44	Week 52	Week 56	Week 60	Week 68	Week 80	Week 92	Week 104	4 Week Post Flare[b]	PD	30-Day Follow Up
INTERVIEWS & QUESTIONNAIRES																							
Subject Information/Informed Consent	✓																						
Eligibility criteria	✓	✓																					
Medical history	✓	✓																					
Alcohol and Nicotine Use	✓																						
Adverse event assessment	✓[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Health Resource Utilization Questionnaire									✓				✓						✓		✓		
TB Risk Assessment Form	✓												✓						✓				
Patient Experience Questionnaire		✓																					
Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Activity	Period 1													Period 2							PD	FU
	Screening	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 44	Week 52	Week 56	Week 60	Week 68	Week 80	Week 92	Week 104	4 Week Post Flare[b]	PD	30-Day Follow Up
PATIENT-REPORTED OUTCOMES																						
FACIT-Fatigue, SF-36		✓			✓	✓			✓				✓						✓			
PGIC, TSQM					✓	✓			✓				✓						✓			
EQ-5D-5L		✓			✓				✓				✓	✓		✓			✓			
Patient Global Assessment (PGA)		✓							✓				✓						✓		✓	
LABS & EXAMS																						
Clinical Laboratory Tests[d] (hematology, chemistry, urinalysis)	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓		✓	✓	✓		✓	✓
Testing of Total Cholesterol, Triglycerides, LDL-C, and HDL-C		✓				✓			✓								✓					
12-lead ECG[e]	✓																					
Chest X-ray (CXR)[f]	✓												✓[g]						✓[g]			
QuantiFERON-TB Gold Test (or Local PPD Skin Test)	✓												✓[h]						✓[h]			
Height (Screening only), Weight	✓	✓				✓			✓				✓				✓		✓		✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical exam	✓	✓				✓			✓				✓				✓		✓		✓	
Assessment of GCA signs & symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Activity	Period 1													Period 2							PD	FU
	Screening	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 44	Week 52	Week 56	Week 60	Week 68	Week 80	Week 92	Week 104	4 Week Post Flare[b]	PD	30-Day Follow Up
Pregnancy Test (Females of child-bearing potential only) Urine (u), Serum (s)[i]	✓ (s)	✓ (u) (s)[j]		✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)	✓ (u)		✓ (u)	✓ (u)
Follicle Stimulating Hormone (FSH) (as applicable)[k]	✓																					
Hepatitis Panel[l]	✓																					
Anti-HIV Ab	✓																					
Lymphocyte Subset		✓								✓			✓						✓		✓	
Erythrocyte Sedimentation Rate (ESR)[m]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
High sensitivity C-reactive protein (hsCRP)[m]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Beta-D-glucan (Japan only)	✓																					
Blood Samples for Upadacitinib PK Assay						✓			✓			✓	✓								✓[n]	
℞ TREATMENT																						
Randomization/Drug Assignment		✓											✓[o]									
Dispense Study Drug, Dosing Instructions[p] and Dosing Diary		✓	✓	✓	✓[q]	✓	✓	✓[q]	✓	✓	✓[q]	✓[q]	✓	✓	✓	✓	✓	✓				
Review Dosing Diary			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Activity	Period 1													Period 2							PD	FU
	Screening	Baseline[a]	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 36	Week 44	Week 52	Week 56	Week 60	Week 68	Week 80	Week 92	Week 104	4 Week Post Flare[b]	PD	30-Day Follow Up
Review Study Drug Return/Reconciliation			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Optional Samples for Biomarker Exploratory Research																						
Pharmacogenetic sample		✓																				
Epigenetic sample		✓	✓			✓			✓				✓									
Transcriptomic sample		✓	✓			✓			✓				✓									
Proteomic and targeted protein investigations sample (serum)		✓	✓			✓			✓				✓									
Proteomic and targeted protein investigations sample (plasma)		✓	✓			✓			✓				✓									

a. The Baseline visit procedures will serve as the reference for all subsequent visits with the exception of the ECG, which will be obtained at Screening only and used as the baseline reference.

b. The 4-week post-flare visit is not applicable for subjects who do not experience a flare of GCA. The 4 week post-flare visit will not be required for subjects who have reassessment of GCA signs and symptoms at a regularly scheduled visit occurring within approximately 4 weeks.

c. Only SAEs and protocol-related nonserious AEs will be recorded during screening.

d. Minimum 8-hour fast. If a subject is not able to fast, the non-fasting status will be recorded in study source documentation.

e. Screening ECG is not required if subjects had normal ECG within 90 days of Screening (refer to Operations Manual Section 3.11 [12-Lead Electrocardiogram] for additional details).

f. Screening CXR is not required if subjects had normal CXR (posterior-anterior and lateral views) within 90 days of *Screening (refer to Operations Manual Section 3.12 [Chest X-Ray]* for additional details).

g. Obtain chest x-ray (CXR) for subjects with TB risk factors as identified by the TB risk assessment form for subjects living in areas endemic for TB or for subjects with a newly-positive QuantiFERON-TB Gold test (and/or purified protein derivative [PPD] skin test) after baseline.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

h. Subjects with a negative TB test result at Screening (or the most recent evaluation) will have an annual TB follow-up test performed, with the same type of TB test used at Screening (e.g., QuantiFERON-TB Gold Test or Local PPD Skin Test), if the subject is still taking the study drug. If an annual TB test is newly positive (seroconversion), a CXR needs to be performed as soon as possible to aid in distinguishing active versus latent TB. During the study, subjects with new evidence of latent TB should initiate prophylactic treatment immediately per local guidelines and complete at least 6 months of prophylaxis (or per local guidelines, whichever is longer). TB prophylaxis should be initiated, and study drug should not be withheld. Two to 4 weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms, as well as laboratory assessment of toxicity to TB prophylaxis. Newly initiated prophylactic treatment should be captured in the eCRF and in the source documents.

i. Women of childbearing potential are required to have monthly pregnancy testing. At Weeks 32, 40, 48, 64, 72, 76, 84, 88, 96, and 100, women of childbearing potential may have an unscheduled office visit for required monthly pregnancy testing or elect to perform the required monthly testing at home with test kits provided by the site. Additional testing may be required per local requirements.

j. Serum pregnancy testing is required at Baseline only if urine pregnancy testing is positive, or if serum pregnancy testing is required at Baseline per local practices.

k. FSH should be tested at Screening if the female subject is ≤ 55 years of age AND has had no menses ≥ 12 months AND has no history of permanent surgical sterilization (Refer to Section 5.2 for further details regarding definition of postmenopausal).

l. For subjects in Japan with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening, HBV DNA PCR test should be performed every 12 weeks (as necessary, unscheduled visits may be needed). HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+, HBc Ab–.

m. After the Baseline Visit, results of hsCRP (central laboratory) will be blinded to the Sponsor, the investigator, the subject, and study site personnel. After the Screening Visit, results of ESR (local laboratory) will be blinded to the Sponsor, the investigator, the subject, and study site personnel with the exception of the local Laboratory Assessor assigned at each study site (see Section 5.7 for additional information).

n. Applies to Period 1 only.

o. Subjects who achieved remission for at least 24 consecutive weeks prior to the Week 52 Visit (at the end of Period 1) will be re-randomized into Period 2. Remission is defined as absence of GCA signs and symptoms AND adherence to the protocol-defined CS taper regimen or corticosteroid-free. At Week 52, subjects who have absence of GCA signs and symptoms AND are CS-free at the Week 52 visit, but do not meet remission criteria (i.e., achieve remission for at least 24 consecutive weeks prior to the Week 52 Visit) will continue in Period 2 on their originally randomized treatment assignment. All other subjects will be discontinued from study drug and the study at the end of Period 1.

p. Dosing instructions will be provided at the Baseline Visit and replaced if lost or damaged.

q. Approximately 2 days prior to each visit with scheduled pharmacokinetic (PK) sample collection, site personnel will contact subjects as reminder to document dosing information on dosing diary and to bring completed dosing diary to the visit. Additional details are provided in the Operations Manual.

Note 1. Visit window is ± 2 days for Period 1 (Week 2 through Week 52 Visit) and ± 2 days for Period 2 (Week 56 through Week 104 Visit). Any of the procedures may be performed at an unscheduled visit at the discretion of the investigator.

Note 2. Subjects who choose to discontinue study drug treatment, but continue to participate in the study, should complete a Premature Discontinuation Visit (PD Visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule for the period from which they discontinue and adhere to all study procedures except for dispensing study drug, or reviewing returns and accountability, dispensing/reviewing study drug instructions, dosing diaries, PK sample collection, and sample collection for exploratory research. That is, subjects who discontinue study drug in Period 1 should complete the visits in Period 1, but not continue to Period 2. Subjects who discontinue study drug in Period 2, should complete the visits in Period 2. In addition, all future CS escape therapy and efficacy-driven discontinuation criteria no longer apply.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX E. CORTICOSTEROID TAPERING SCHEDULE

	Blinded 52-Wk Costicosteroid* Taper (Dose in mg)				
Baseline	**20**	**30**	**40**	**50**	**60**
Wk 1	17	25	35	40	50
Wk 2	17	20	30	35	40
Wk 3	15	17	25	30	35
Wk 4	15	17	20	25	30
Wk 5	12	15	17	20	25
Wk 6	10	15	17	17	20
Wk 7	10	12	15	17	17
Wk 8	10	10	15	15	17
Wk 9	10	10	12	15	15
Wk 10	9	10	10	12	15
Wk 11	9	10	10	10	12
Wk 12	9	9	10	10	10
Wk 13	9	9	10	10	10
Wk 14	8	9	9	10	10
Wk 15	8	9	9	9	10
Wk 16	8	8	9	9	9
Wk 17	8	8	9	9	9
Wk 18	7	8	8	9	9
Wk 19	7	8	8	8	9
Wk 20	7	7	8	8	8
Wk 21	7	7	8	8	8
Wk 22	6	7	7	8	8
Wk 23	6	7	7	7	8
Wk 24	6	6	7	7	7
Wk 25	6	6	7	7	7
Wk 26	5	6	6	7	7
Wk 27	5	6	6	6	7
Wk 28	5	5	6	6	6
Wk 29	5	5	6	6	6
Wk 30	4	5	5	6	6
Wk 31	4	5	5	5	6
Wk 32	4	4	5	5	5
Wk 33	4	4	5	5	5
Wk 34	3	4	4	5	5
Wk 35	3	4	4	4	5
Wk 36	3	3	4	4	4
Wk 37	3	3	4	4	4
Wk 38	2	3	3	4	4
Wk 39	2	3	3	3	4
Wk 40	2	2	3	3	3
Wk 41	2	2	3	3	3
Wk 42	1	2	2	3	3
Wk 43	1	2	2	2	3
Wk 44	1	1	2	2	2
Wk 45	1	1	2	2	2
Wk 46	0	1	1	2	2
Wk 47	0	1	1	1	2
Wk 48	0	0	1	1	1
Wk 49	0	0	1	1	1
Wk 50	0	0	0	1	1
Wk 51	0	0	0	0	1
Wk 52	0	0	0	0	0

	Blinded 26-Wk Corticosteroid* Taper (Dose in mg)				
Baseline	**20**	**30**	**40**	**50**	**60**
Wk 1	15	25	35	40	50
Wk 2	12	20	30	35	40
Wk 3	12	15	25	30	35
Wk 4	10	12	20	25	30
Wk 5	9	12	15	20	25
Wk 6	8	10	12	15	20
Wk 7	7	9	12	12	15
Wk 8	6	8	10	12	12
Wk 9	6	7	9	10	12
Wk 10	5	6	8	9	10
Wk 11	5	6	7	8	9
Wk 12	4	5	6	7	8
Wk 13	4	5	6	6	7
Wk 14	3	4	5	6	6
Wk 15	3	4	5	5	6
Wk 16	2	3	4	5	5
Wk 17	2	3	4	4	5
Wk 18	1	2	3	4	4
Wk 19	1	2	3	3	4
Wk 20	0	1	2	3	3
Wk 21	0	1	2	2	3
Wk 22	0	0	1	2	2
Wk 23	0	0	1	1	2
Wk 24	0	0	0	1	1
Wk 25	0	0	0	0	1
Wk 26	0	0	0	0	0
Wk 27	0	0	0	0	0
Wk 28	0	0	0	0	0
Wk 29	0	0	0	0	0
Wk 30	0	0	0	0	0
Wk 31	0	0	0	0	0
Wk 32	0	0	0	0	0
Wk 33	0	0	0	0	0
Wk 34	0	0	0	0	0
Wk 35	0	0	0	0	0
Wk 36	0	0	0	0	0
Wk 37	0	0	0	0	0
Wk 38	0	0	0	0	0
Wk 39	0	0	0	0	0
Wk 40	0	0	0	0	0
Wk 41	0	0	0	0	0
Wk 42	0	0	0	0	0
Wk 43	0	0	0	0	0
Wk 44	0	0	0	0	0
Wk 45	0	0	0	0	0
Wk 46	0	0	0	0	0
Wk 47	0	0	0	0	0
Wk 48	0	0	0	0	0
Wk 49	0	0	0	0	0
Wk 50	0	0	0	0	0
Wk 51	0	0	0	0	0
Wk 52	0	0	0	0	0

Open-label taper until 20 mg

*Prednisone or Prednisolone

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	27 March 2018
Version 2.0	05 September 2018
Version 2.1 (VHP)	15 February 2019
Version 3.0	28 March 2019
Version 4.0	27 March 2020
Version 5.0	09 December 2020
Administrative Change 1	13 October 2021
Version 6.0	29 March 2022
Administrative Change 2 (Japan Only)	08 August 2022

Summary of Protocol Changes:

The following changes were made in Version 7.0 of this protocol:

Protocol

- Title page, Footer: Added EU CT number.

  Rationale: *To provide EU CT number.*

- Section 1, Synopsis: Updated Objectives and Endpoints, Study Drug and Duration of Treatment, date.

  Rationale: *To align with protocol updates.*

- Section 2.2, Benefits and Risks to Patients: Updated AEs observed in patients receiving JAK inhibitors, added results of ORAL Surveillance study, a study of a different JAK inhibitor.

  Rationale: *To align with known AEs and to provide additional detail based on the ORAL Surveillance study to support the current research.*

- Section 3.3, Secondary Endpoints: Updated title to Multiplicity-Controlled Secondary Endpoints and Additional Endpoints.

  Rationale: To clarify that the secondary endpoints will be multiplicity-controlled.

- Section 3.3, Secondary Endpoints: Updated language of several of the endpoints.

  Rationale: *For correction, clarification, and/or alignment without actual change to the definitions of the existing endpoints.*

- Section 3.3, Secondary Endpoints; Section 7.3, Statistical Analyses for Efficacy; Appendix D, Activity Schedule: Updated FACIT-F to FACIT-Fatigue.

  Rationale: *To clarify FACIT-Fatigue (13 item) is the PRO being used in this trial.*

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Section 5.2, Contraception Recommendations
  - Updated criteria for FSH levels for postmenopausal females.

    Rationale: *To align with criteria for postmenopausal females.*
  - Added language for contraceptive counseling.

    Rationale: *To clarify contraception requirements in subjects whose childbearing potential changes during the study.*
- Section 5.3, Prohibited Medications and Therapy:
  - Updated lists of prohibited biologic therapies, prohibited JAK inhibitors, examples of live vaccines, and examples of commonly used strong CYP3A inhibitors and inducers. Indicated that viral vaccines that cannot replicate are not prohibited and that herbal therapies and other traditional medicines with unknown effects on CYP3A are prohibited.

    Rationale: *To update the lists of prohibited biologic therapies and JAK inhibitors to align with currently approved medications, to align with current knowledge of CYP3A inhibitors and inducers, and to clarify that live vaccines without replicating potential are permitted during the study.*
- Section 5.5, Discontinuation from Study Drug or Subject Withdrawal from Study:
  - Updated malignancy language.

    Rationale: *To clarify that subjects with non-melanoma skin cancer and carcinoma in situ of the cervix may only remain in the study if the cancer can be successfully removed at its localization.*
  - Removed language that the AbbVie TA MD may mandate individual subject discontinuation.

    Rationale: *To minimize the introduction of bias if discontinuation is requested without clear safety criteria for discontinuation.*
  - Updated language for study termination.

    Rationale*: For clarification that advanced notice is not required for study termination.*
- Section 5.6, Follow-Up for Study Drug Discontinuation or Subject Withdrawal from Study: updated description of 30-day follow-up visit to indicate treatment-emergent AEs/SAEs.

  Rationale*: For clarification that only treatment-emergent AEs will be reviewed during the follow-up visit.*
- Section 5.7, Assessment of Disease Activity: Indicated that hsCRP will remain masked until the end of the study for the investigators, site staff and subjects, and that the Sponsor will be unmasked to the hsCRP results at the time of primary analysis.

  Rationale: *To clarify the current language to ensure we maintain the integrity of the blind.*
- Section 5.8, Study Drug: Updated disease flare definition ESR measurement to ≥ 30 mm.

  Rationale*: To correct inconsistencies throughout protocol and operations manual documents.*
- Section 6.1, Complaints and Adverse Events:
  - Added language to describe electronic data capture (EDC) reporting.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Rationale: *To align with electronic data capture procedures.*

- Updated language for SAE reporting.

  Rationale: *To align with SAE reporting to AbbVie clinical pharmacovigilance.*

- Added language for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting.

  Rationale: *To align with SUSAR reporting procedures.*

- Added retinal detachment and bone fracture as AEs that will be monitored during the study.

  Rationale: *To align with updates to the AEs monitored per regulatory request.*

- Section 6.2, Toxicity Management: Added language for muscle-related symptoms, Updated language for COVID-19, Updated guidelines for AST or ALT, Updated guidelines for creatine phosphokinase, indicated that the medical monitor and not the TA MD should be contacted if CPK ≥ 4 × ULN is accompanied by symptoms suggestive of myositis or rhabdomyolysis.

  Rationale: *To provide clarification of study drug management for respective events*

  - Updated language for urgent and emergency surgeries.

    Rationale: *To clarify the circumstances under which elective surgeries may be considered.*

- Section 7.2, Definition for Analysis Populations: Clarified that the FAS in Period 2 is defined as all subjects who achieved sustained remission for at least 24 consecutive weeks prior to Week 52 visit.

  Rationale*: For clarification.*

- Section 7.3, Statistical Analyses for Efficacy: Added language for NRI-MI.

  Rationale: *To align with statistical approaches to handling missing data.*

- Appendix D, Activity Schedule: Indicated that for subjects with a negative TB test at Screening or most recent evaluation, an annual TB re-test will be performed if subject is still taking study drug.

  Rationale: *For clarification that re-test is only performed if subject is still taking study drug.*

Operations Manual

- Section 2.1, Individual Treatment Period Visit Activities: Updated 30-day Follow-Up visit to include phone call, updated description of 30-day follow-up visit to indicate treatment-emergent AEs/SAEs, indicated that for subjects with a negative TB test at Screening or most recent evaluation, an annual TB re-test will be performed if subject is still taking study drug.

  Rationale*: To allow more flexibility if there are no safety issues necessitating an in-person visit, and for clarification that only treatment-emergent AEs will be reviewed during the follow-up visit.*

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Section 2.1, Individual Treatment Period Visit Activities; Section 3.6, Quality of Life and Patient-Reported Outcomes; Appendix C, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) Scale Example: Updated FACIT-F to FACIT-Fatigue.

  Rationale: *To clarify FACIT-Fatigue (13 item) is the PRO being used in this trial.*

- Section 3.10, Vital Signs: indicated that blood pressure, pulse rate, body temperature, and respiratory rate should preferably be performed before blood draws are performed.

  Rationale: *For clarification on timing of procedures related to collecting vital signs.*

- Section 3.12, Chest X-Ray (CXR): Clarified language for assessment of CXR to rule out active TB.

  Rationale: *To clarify CXR procedures associated with TB assessment.*

- Section 3.18, Clinical Laboratory Tests:
  - Updated standard of care to be applied by the investigator for laboratory test values outside of the reference range related to AE reporting.

    Rationale: *To clarify when an abnormal laboratory test should be considered an AE*.

  - Updated disease flare definition from > 30 mm/hr to ≥ 30 mm/hr, indicated where the investigator and the independent ESR assessor should document the ESR result, and clarified that the ESR results will be entered by a person who is not doing the clinical assessment.

    Rationale: *Clarification about where to document communications between the laboratory assessor and the investigator regarding ESR ≥ 30 or < 30, clarification about who should enter the actual ESR values and when they should be entered (to reduce the risk of investigator bias).*

  - Updated pregnancy testing.

    Rationale: *For clarification on procedures related to pregnancy testing.*

  - Indicated that for TB testing, the investigator has the responsibility to follow local guidelines in the detection and treatment of active or latent TB, Updated language for positive TB assessment.

    Rationale: *For clarification on procedures related to TB laboratory testing.*

  - Indicated that for subjects with a negative TB test at Screening or most recent evaluation, an annual TB re-test will be performed if subject is still taking study drug.

    Rationale: *For clarification that re-test is only performed if subject is still taking study drug.*

- Section 4.1, Methods of Timing and Safety Assessment: added eCRFs for Bone Fracture and Retinal Detachment.

  Rationale: *To comply with health authority request.*

- Section 4.3, Reporting Adverse Events and Intercurrent Illnesses: Added contact for safety concerns.

  Rationale: *To align with appropriate safety contact information.*

- Section 5.1, Additional Contraception-Related Eligibility Criteria and Requirements for Canada: updated criteria to indicate that a female subject of childbearing potential must be practicing 2

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

forms of contraception from Baseline through at least 30 days after the last dose of study drug, updated ages for postmenopausal definitions.

Rationale: *For correction and internal consistency within the document.*

- Updated description of "double barrier" methods of contraception to clarify that the double marrier method is not considered a highly effective method of contraception

  Rationale: *To align with CTFG guidance.*

- Added Section 5.3, Japan-Specific Requirements, added reference to Section 5.3 in Section 5.4.

  Rationale: *To align with requirements for study drugs for which safety information is reported in Japan.*

- Section 6.4, Selection and Timing of Dose for Each Subject: Updated language regarding how to handle an interruption of upadacitinib/matching PBO dosing > 14 consecutive days during the first 24 weeks or > 21 consecutive days after Week 24.

  Rationale*: To advise discussion with TA MD before discontinuation.*

In addition to the above modifications, this Amendment contains minor text edits as needed for consistency and clarity.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.