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Protocol for Study M19-051

Evaluation of Upadacitinib in Subjects with Non-Segmental Vitiligo

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FULL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Non-Segmental Vitiligo

Incorporating Versions 1.0 and 2.0

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

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1 SYNOPSIS

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Non-Segmental Vitiligo	
Background and Rationale:	Vitiligo is a common chronic autoimmune disorder of the skin characterized by depigmented skin lesions due to autoimmune-induced loss of melanocytes in the epidermis. The disease is associated with an impaired quality of life. There is no approved medical therapy for vitiligo re-pigmentation and current unapproved therapies have limited efficacy, emphasizing the need for improved treatment options. In 2011, an international consensus classified vitiligo into segmental vitiligo and non-segmental vitiligo (NSV), with the majority of patients (> 90%) exhibiting the non-segmental variant. Segmental vitiligo refers to depigmented macules and patches distributed in a segmental or unilateral pattern, whereas NSV lesions are distributed bilaterally. In general, the term vitiligo is being used to describe all forms of NSV, which includes acrofacial, mucosal, generalized, universal, mixed, and rare variants. Evidence suggests that inhibition of Janus kinase (JAK)-mediated pathways may be a promising approach for the treatment of patients with vitiligo. Ruxolitinib (a JAK1/2 inhibitor), in a topical formulation, has demonstrated efficacy in treating patients with vitiligo in a Phase 2 study and is currently enrolling patients in two Phase 3 studies. AbbVie developed a JAK inhibitor, upadacitinib, which, when given systemically may address the current needs for patients with vitiligo. Upadacitinib is a selective and reversible inhibitor of JAK1 that recently has received approval for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis in some countries and is also being developed for the treatment of other immune-mediated inflammatory diseases, including dermatologic conditions such as atopic dermatitis and hidradenitis suppurativa.
Objective(s) and Endpoint(s):	**Objective:** The primary objective of this study is to evaluate the safety and efficacy of upadacitinib for the treatment of adult subjects with NSV. **Primary Endpoint:** The primary endpoint is the percent change from Baseline in Facial Vitiligo Area Scoring Index (F-VASI) at Week 24.
Investigator(s):	Multi-center
Study Site(s):	Approximately 35 sites
Study Population and Number of Subjects to be Enrolled:	Approximately 160 adult subjects with NSV

Investigational Plan:	The study is comprised of a 35-day Screening Period, a 24-week double-blind treatment period (Period 1), a 28-week blinded long-term extension (Period 2), and a 30-day Follow-up Period. Subjects who meet eligibility criteria at Baseline will be randomized in a 2:2:2:1:1 ratio to one of five treatment groups: • Group 1: upadacitinib 22 mg once daily (QD) (N = 40) (Period 1) → upadacitinib 22 mg QD (Period 2) • Group 2: upadacitinib 11 mg QD (N = 40) (Period 1) → upadacitinib 11mg QD (Period 2) • Group 3: upadacitinib 6 mg QD (N = 40) (Period 1) → upadacitinib 6 mg QD (Period 2) • Group 4: placebo (N = 20) (Period 1) → upadacitinib 22 mg QD (Period 2) • Group 5: placebo (N = 20) (Period 1) → upadacitinib 11 mg QD (Period 2) At Week 24, subjects who were randomized to placebo at Baseline will be switched to either 22 mg (Group 4) or 11 mg (Group 5) upadacitinib in a blinded fashion per pre-specified randomization assignments. Study visits may be impacted due to the coronavirus disease 2019 (COVID-19) pandemic. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others, may be performed. Additional details are provided in the subsequent sections of the protocol. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study.
Key Eligibility Criteria:	Eligible subjects will be adult females and males ≥ 18 to 65 years of age at Screening with a clinical diagnosis of NSV and no segmental or localized vitiligo, with all of the following at Screening and Baseline Visits: ≥ 0.5 F-VASI and ≥ 5 total Vitiligo Area Scoring Index (T-VASI). Subjects with other skin conditions that would interfere with evaluation of vitiligo, subjects with uncontrolled thyroid disease, and subjects with > 33% leukotrichia on the face or > 33% leukotrichia on the body (including face) are not eligible to enroll in this study. Eligible subjects must not have previously been treated with any topical or systemic JAK inhibitor. Also, subjects must not have been previously treated with any permanent skin bleaching agents to treat vitiligo. Subjects must not have been treated with any systemic vitiligo therapy (e.g., methotrexate, mycophenolate mofetil, corticosteroids), supplemental vitiligo therapy (antioxidants/vitamins/herbal medicine/traditional Chinese medicine), and/or topical vitiligo therapy including permanent or temporary tattoos within a minimum of 30 days prior to the first dose of study drug (Note: Camouflage and makeup may be used). Eligible subjects must not have been treated with any phototherapy, including excimer (or other forms of laser therapy), within a minimum of 12 weeks prior to the first dose of study drug. Subjects who have had prior exposure to immunomodulatory

	biologic therapy, for any indications, must have discontinued the biologic therapy prior to the first dose of study drug. Recommended washout periods for biologic therapies include ≥ 4 weeks for etanercept; ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and ixekizumab; ≥ 16 weeks for secukinumab; and ≥ 12 weeks for ustekinumab. For biologic therapies not specified, therapies must be discontinued at least 5 times the mean terminal elimination half-life of a drug or 3 months prior to Baseline, whichever is longer.
Study Drug and Duration of Treatment:	Upadacitinib 6 mg QD extended-release, film-coated tablets for oral administration, 52 weeks in duration. Upadacitinib 11 mg or 22 mg QD extended-release, film-coated tablets for oral administration, 28 or 52 weeks in duration. Placebo for upadacitinib QD film-coated tablets for oral administration, 24 weeks in duration.
Date of Protocol Synopsis:	07 July 2021

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Vitiligo is a common chronic autoimmune disorder of the skin characterized by depigmented skin lesions due to autoimmune-induced loss of melanocytes in the epidermis.[1] The disease is associated with an impaired quality of life (QoL).[2] There is no approved medical therapy for vitiligo re-pigmentation and current unapproved therapies have limited efficacy, emphasizing the need for improved treatment options.

The disease most commonly presents as white macules and patches of skin with equal impact on men and women.[3] Vitiligo manifests as milky-white patches of pigment loss due to localized melanocyte destruction. Early depigmentation typically occurs on the face and extremities. In 2011, an international consensus classified vitiligo into segmental vitiligo and non-segmental vitiligo (NSV), with the majority of patients (> 90%) exhibiting the non-segmental variant.[4] Segmental vitiligo refers to depigmented macules and patches distributed in a segmental or unilateral pattern, whereas NSV lesions are distributed bilaterally.[4] In general, the term vitiligo is being used to describe all forms of NSV, which includes acrofacial, mucosal, generalized, universal, mixed, and rare variants.

The global prevalence of vitiligo is approximately 0.5% to 2%, and patients with vitiligo often have psychological and autoimmune comorbidities.[2,5,6] Vitiligo has been associated with several auto-immune diseases such as thyroid disease (Hashimoto thyroiditis), psoriasis, rheumatoid arthritis (RA), alopecia areata, pernicious anemia, systemic lupus erythematosus, and diabetes mellitus. It has also been associated with inflammatory bowel disease and sometimes ocular and audiological abnormalities.[7,8] Although patients with vitiligo have a decreased risk of melanoma and non-melanoma skin cancer (NMSC),[9,10] clinical practice recommends constant use of sunscreen due to the risks of sunburn from direct sunlight on depigmented skin. Overall, the effect of vitiligo on QoL impairment seem to be associated with the distribution of vitiligo lesions (e.g., face, genital area) but also by the extent of the disease, highlighting the unmet need of effective systemic therapies.

There are few treatment options for vitiligo and these have limited efficacy. Thus, there is a lack of options for patients with vitiligo, particularly those with severe manifestation of the disease, given the limited response to currently available topical and systemic therapies.

Impairment or death of melanocytes is believed to be the direct cause of vitiligo. Melanocytes produce the pigment melanin, which colors the skin and provides protection from UV radiation. While several theories describe vitiligo pathogenesis, the exact etiology is unknown. The autoimmune theory hypothesizes that interferon (IFN)-y is an important cytokine expressed in lesional skin and is required for the recruitment of melanocyte-specific, autoreactive CD8+ T cells to the skin via the chemokines CXCL9/10 and CXCR3.[11,12] Cytotoxic CD8+ T cells are both necessary and sufficient for melanocyte destruction in the skin of vitiligo patients and therefore serve as the effector arm driving the autoimmunity of vitiligo. The Janus kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) pathway is therefore an attractive therapeutic target due to its direct effect on IFN-y and CXCL10 levels.

Evidence suggests that inhibition of JAK-mediated pathways may be a promising approach for the treatment of patients with vitiligo.[13] Ruxolitinib (a JAK1/2 inhibitor), in a topical formulation, has demonstrated efficacy in treating patients with vitiligo in a Phase 2 study[14] and is currently enrolling patients in two Phase 3 studies.[15,16] AbbVie developed a JAK inhibitor, upadacitinib, which, when given systemically may address the current needs for patients with vitiligo. Upadacitinib is a selective and reversible inhibitor of JAK1 that recently has received approval for the treatment of RA, psoriatic arthritis (PsA), and ankylosing spondylitis (AS) in some countries and is also being developed for the treatment of other immune-mediated inflammatory diseases, including dermatologic conditions such as atopic dermatitis (AD) and hidradenitis suppurativa.

Clinical Hypothesis

Vitiligo is a chronic autoimmune disorder of the skin characterized by an increase of proinflammatory cytokines involved in the JAK/STAT pathway. Upadacitinib is predicted to provide better efficacy compared to placebo and to be well tolerated in vitiligo subjects.

2.2 Benefits and Risks to Subjects

Currently there are no approved medical therapies for skin re-pigmentation for patients with vitiligo and current unapproved therapies such as topical corticosteroids and calcineurin inhibitors have limited efficacy, indicating that there is a high unmet need. Phototherapy is one of the most common therapies used for vitiligo; nonetheless, treatment can be burdensome to patients as it requires multiple and frequent visits to the office or home therapy and is associated with a high relapse rate within the first year upon discontinuation (average 40%), highlighting the need for long-lasting therapies.[17]

At this time, patients with significant vitiligo, including patients with rapidly progressive disease, are commonly treated with oral steroids which are not suitable for long-term use.

The efficacy of upadacitinib has shown promising results in various immune-mediated diseases including dermatologic conditions such as AD.[18]

Adverse events (AEs) such as infections, herpes zoster reactivation, malignancies, and hematologic AEs have been observed in patients receiving JAK inhibitors including upadacitinib. The available long-term safety data from the Phase 3 RA studies with upadacitinib showed an increased risk of infection including opportunistic infections (e.g., mucosal candida infections) and herpes zoster, as well as abnormal laboratory changes have been observed (e.g., elevations of serum transaminases, lipids, creatine phosphokinase [CPK], and reductions in hemoglobin and white blood cells [WBCs]) with upadacitinib therapy. The incidence rates of other clinically important AEs such as cardiovascular events, malignancies, and mortality reported during the RA studies were within the expected range for the general population or for a population of patients with moderately to severely active RA.[19] Events of deep vein thrombosis (DVT) and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. Similar findings of these important AEs were also observed in the clinical studies for other indications including PsA and AD. AEs of acne have been observed more frequently with upadacitinib treatment versus placebo in Phase 3 PsA and AD studies.

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.[19]

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 immune-mediated inflammatory conditions including vitiligo.

In view of the coronavirus disease 2019 (COVID-19) 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 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective of this study is to evaluate the safety and efficacy of upadacitinib for the treatment of adult subjects with NSV.

The primary efficacy objective is based on the percent change from Baseline in Facial Vitiligo Area Scoring Index (F-VASI) at Week 24 with upadacitinib treatment compared to placebo in the Intent-to-Treat (ITT) Population, which consists of all randomized subjects (Section 7.2).

The hypothesis corresponding to the primary endpoint (Section 3.2) is:

- Percent change from Baseline in F-VASI with upadacitinib is greater than that with placebo at Week 24.

The estimand corresponding to the primary endpoint is defined as:

- Difference in the percent change from Baseline in F-VASI at Week 24, regardless of treatment discontinuation, between each of the upadacitinib dose groups compared with placebo in the ITT Population.

3.2 Primary Endpoint

The primary endpoint is the percent change from Baseline in F-VASI at Week 24.

3.3 Secondary Endpoints

Secondary Endpoints

1. Achievement of F-VASI 75 (≥ 75% improvement in F-VASI from Baseline) at Week 24;
2. Achievement of F-VASI 50 (≥ 50% improvement in F-VASI from Baseline) at Week 24;
3. Achievement of total Vitiligo Area Scoring Index (T-VASI) 50 (≥ 50% improvement in T-VASI from Baseline) at Week 24;
4. Percent change from Baseline in T-VASI at Week 24;
5. Change from Baseline in the vitiligo quality-of-life (VitiQoL) instrument total score at Week 24.

3.4 Additional Endpoints

Additional Efficacy Endpoints include the primary and all secondary endpoints assessed at visits as noted in the Activity Schedule (Appendix D), other than Week 24. Additional Efficacy Endpoints also include the following measurements assessed at visits as specified in the Activity Schedule:

- Achievement of F-VASI 90 (≥ 90% improvement in F-VASI from Baseline);
- Achievement of T-VASI 75 (≥ 75% improvement in T-VASI from Baseline);
- Achievement of T-VASI 90 (≥ 90% improvement in T-VASI from Baseline);
- Mean and percent change from Baseline in the vitiligo extent score (VES);
- Achievement of vitiligo noticeability scale (VNS) score of "A lot less noticeable (4)" or "No longer noticeable (5)";
- Dermatology Life Quality Index (DLQI) total score of "0" or "1";
- Change from Baseline in the Hospital Anxiety and Depression Scale (HADS) scores;
- Proportion of subjects selecting each of the response categories of VitiQoL 16 questions;
- Achievement of Physician's Global Impression of Change-Vitiligo (PhGIC-V) of "Much better (1)" or "A little better (2)";
- Achievement of Patient's Global Impression of Change-Vitiligo (PaGIC-V) of "Much better (1)" or "A little better (2)";
- Achievement of Face – Physician Global Vitiligo Assessment (F-PhGVA) of "No depigmentation (0)" or "Limited extent of depigmentation (1)";
- Achievement of Total – Physician Global Vitiligo Assessment (T-PhGVA) of "No depigmentation (0)" or "Limited extent of depigmentation (1)";
- Achievement of Face – Patient Global Vitiligo Assessment (F-PaGVA) of "No depigmentation (0)" or "Limited extent of depigmentation (1)";
- Achievement of Total – Patient Global Vitiligo Assessment (T-PaGVA) of "No depigmentation (0)" or "Limited extent of depigmentation (1)."

Details on efficacy variables are provided in the operations manual (Appendix F).

3.5 Safety Endpoints

Safety evaluations include AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), AEs leading to discontinuation, vital signs, laboratory tests (hematology, chemistry, liver function tests), and physical examination.

3.6 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples will be obtained at specified clinic visits as noted in Appendix D. Upadacitinib plasma concentrations will be determined and summarized in the clinical study report. In addition, a nonlinear mixed-effects modeling approach may be used to estimate the population central values and the empirical Bayesian estimates of the individual values of upadacitinib PK parameters (e.g., oral clearance [CL/F] and apparent volume of distribution [V/F]). Data from this study may be combined with data from other studies for the population PK analyses.

3.7 Biomarker Research Endpoints

Optional samples for biomarker research (e.g., whole blood, plasma, serum, and skin biopsies) will be collected at specified time points (Activity Schedule, Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Types of biomarkers may include nucleic acids, proteins, cell populations, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to soluble proteins, genomic transcripts, blood leukocyte populations, and genetic analysis to evaluate biomarker endpoints related to safety, disease state, and target pathway. Results from this optional biomarker research may not be included in the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the operations manual, Appendix F, Section 3.12.

3.8 Exploratory and/or Validation Research

Digital Imaging

Validation of a 3-D digital imaging tool will be explored at a subset of sites to objectively quantify the surface area of vitiligo lesions (depigmentation) on the face with precision. Approximately 5 sites will be selected to participate in the digital imaging research. Once the digital imaging platform is available for implementation at the selected sites, all subjects enrolled thereafter will be required to participate. The results from these analyses are exploratory in nature and may not be included with the clinical study report.

Individual Component Vitiligo Assessment (ICVA)

The ICVA will be used to collect exploratory information regarding vitiligo involvement on the genitals and individual components of the face using 2 assessments: Physician Global Vitiligo Assessment

(PhGVA) and how much vitiligo lesions are bothersome to subjects. The results from these analyses are exploratory in nature and may not be included with the clinical study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, multicenter, randomized, double-blinded, parallel-group, placebo-controlled dose-ranging study that will evaluate the safety and efficacy of upadacitinib in adult subjects ≥ 18 to 65 years of age with NSV. The study is comprised of a 35-day Screening Period, a 24-week double-blind treatment period (Period 1), a 28-week blinded long-term extension (Period 2), and a 30-day Follow-up Period.

Subjects who meet eligibility criteria at Baseline will be randomized in a 2:2:2:1:1 ratio to one of five treatment groups:

- Group 1: upadacitinib 22 mg once daily (QD) (N = 40) (Period 1) → upadacitinib 22 mg QD (Period 2)
- Group 2: upadacitinib 11 mg QD (N = 40) (Period 1) → upadacitinib 11mg QD (Period 2)
- Group 3: upadacitinib 6 mg QD (N = 40) (Period 1) → upadacitinib 6 mg QD (Period 2)
- Group 4: placebo (N = 20) (Period 1) → upadacitinib 22 mg QD (Period 2)
- Group 5: placebo (N = 20) (Period 1) → upadacitinib 11 mg QD (Period 2)

At Week 24, subjects who were randomized to placebo at Baseline will be switched to either 22 mg (Group 4) or 11 mg (Group 5) upadacitinib in a blinded fashion per pre-specified randomization assignments.

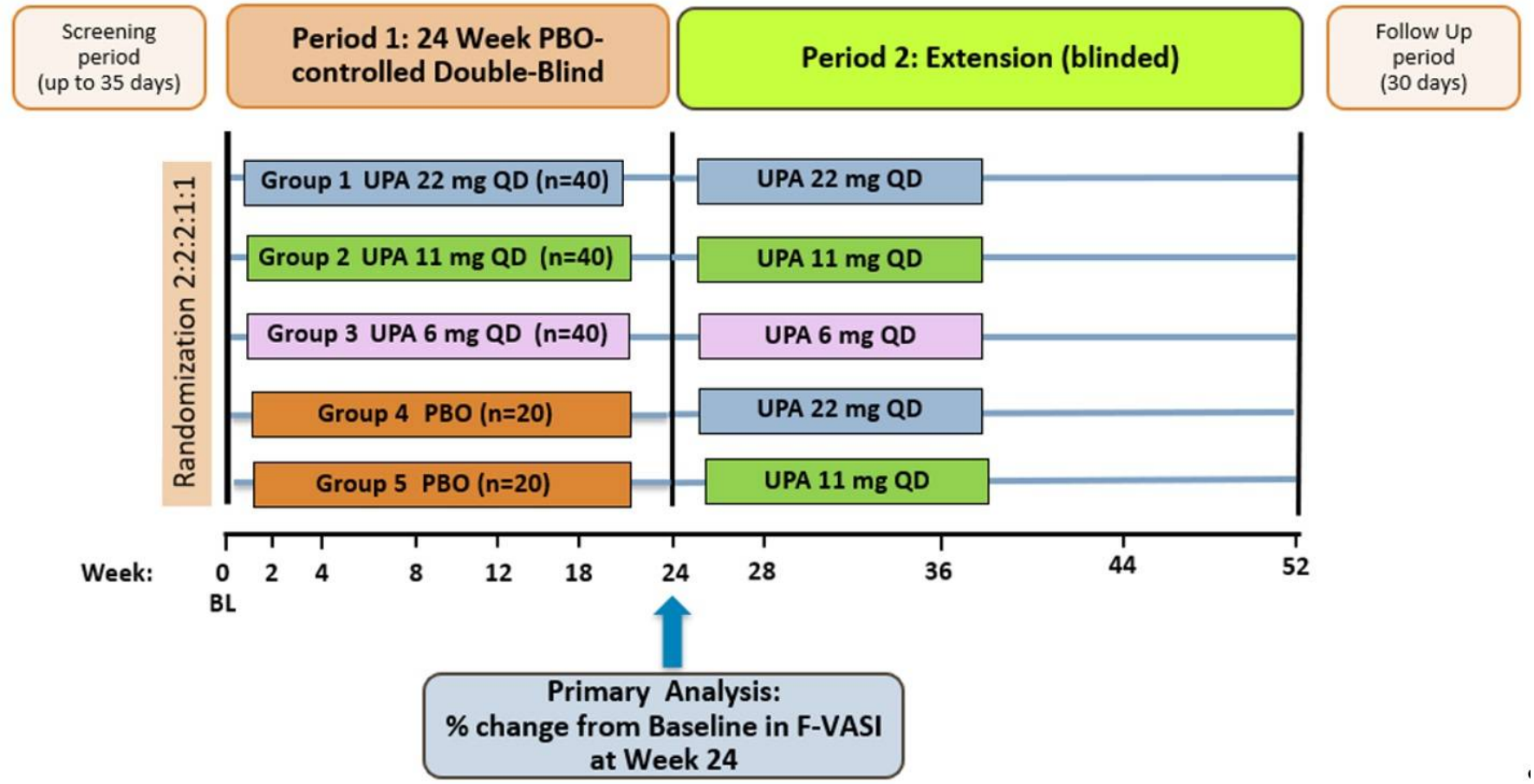
The AbbVie study team will be unblinded to perform the Week 24 primary analysis. The unblinding will take place after all subjects have completed the Week 24 visit or have prematurely discontinued prior to Week 24. Sites and subjects will remain blinded throughout the study.

Information on the Data Monitoring Committee (DMC) is described in Section 6.3. Information on the Cardiovascular Adjudication Committee (CAC) and gastrointestinal (GI) perforation adjudication are described in Section 6.1.

See Section 5.1 for information regarding eligibility criteria and Section 5.8 for information on stratification.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the operations manual (Appendix F).

Figure 1. Study Schematic



BL = Baseline; F-VASI = Facial Vitiligo Area Scoring Index; PBO = placebo; QD = once daily; UPA = upadacitinib

4.2 Discussion of Study Design

Choice of Control Group

Placebo control will be used in this study. Comparative studies utilizing a double-blind, placebo-controlled design provides an unbiased assessment of the efficacy and safety profile of upadacitinib.

Appropriateness of Measurements

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

Care should be taken to minimize the pain and discomfort of laboratory procedures. Use of a butterfly needle for venipuncture and/or a needle gauge appropriate for vein size may optimize the comfort for some individuals. Attempts at venipuncture should be limited to the subject's tolerance of the procedure; after more than 2 unsuccessful attempts for venipuncture, consider requesting the subject to return within the next 3 days if still within the visit window and after drinking plenty of fluids (1 L to 2 L over a 24-hour period).

Suitability of Subject Population

The intended study population is adult subjects ≥ 18 to 65 years of age with NSV. Subjects with documented clinical diagnosis of NSV and no segmental or localized vitiligo are eligible for this study. At study entry, eligible subjects must have at least 0.5 F-VASI and at least 5 T-VASI. Criteria relating to safety have been selected to allow subjects to be safely enrolled and treated with upadacitinib based on the current knowledge of this drug.

Selection of Doses in the Study

This study is designed as a dose-ranging study to evaluate upadacitinib doses of 6 mg, 11 mg, and 22 mg QD in adult subjects with vitiligo. These doses were selected to provide comprehensive dose-ranging information in patients with vitiligo through evaluation of upadacitinib doses that have not been studied in other upadacitinib indications (e.g., RA, PsA, AS, and AD).

Patients with vitiligo generally present with a clinically (and biologically) different disease profile compared to previously studied indications for upadacitinib. Although vitiligo significantly impairs QoL, it is generally considered an asymptomatic dermatosis (some patients may suffer from skin irritation/itching), and is usually associated with lower comorbidities, minimal background and concomitant therapies, and less heterogeneous signs and symptoms of the disease. Hence, the upadacitinib dose(s) that may provide optimal benefit risk in patients with vitiligo are yet to be determined and may occur at dose levels that have not been previously explored for other indications.

Upadacitinib 15 mg QD and 30 mg QD doses showed significant clinical benefit for treatment of subjects with RA, PsA, AS, and AD in Phase 3 studies, with an added clinical benefit of 30 mg compared to 15 mg for some (e.g., AD) but not all (e.g., RA, PsA) indications.

Two case studies have reported partial re-pigmentation of vitiligo white patches after administration of tofacitinib, a pan JAK-inhibitor, at a 5 mg twice a day dose together with narrowband UV-B therapy.[20] Although the observed response in these 2 case studies was achieved with a combination of tofacitinib and phototherapy, the findings suggest that JAK inhibition with dose levels comparable to efficacious doses in RA and PsA populations may provide clinical efficacy in patients with vitiligo. Whether lower or higher doses could provide similar or higher efficacy, respectively, remains unclear and requires more data from adequate dose-ranging studies in patients with vitiligo.

Hence, upadacitinib doses of 11 mg and 22 mg have been selected to allow evaluation of upadacitinib exposure levels below and above the 15 mg dose, respectively, that have not been evaluated in other indications. The proposed 11 mg and 22 mg doses are expected to provide upadacitinib exposures that partially overlap with those achieved with the 15 mg dose, but at the same time provide enough separation between the doses to enable adequate characterization of the dose/exposure-response relationship. The 6 mg dose was selected to ensure characterization of the minimally efficacious dose in the vitiligo patient population.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

- 1. Subject must be able to understand and willing to adhere to all protocol requirements and voluntarily **sign and date an informed consent**, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographics

- 2. Adult (**male or female**) ≥18 to 65 years of age.

Disease/Condition Activity

- 3. Documented clinical diagnosis of NSV.
- 4. At Screening and Baseline visits, subjects must have ≥ 0.5 F-VASI AND ≥ 5 T-VASI.
- 5. No segmental or localized vitiligo.

Laboratory Assessments

- 6. **Laboratory values** meeting the following criteria within the Screening Period prior to the first dose of study drug:

- Serum aspartate transaminase (AST) ≤ 2 × upper limit of normal (ULN);
- Serum alanine transaminase (ALT) ≤ 2 × ULN;
- Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula;
- Total WBC count ≥ 2,500/µL;
- Absolute neutrophil count (ANC) ≥ 1,200/µL;
- Platelet count ≥ 100,000/µL;
- Absolute lymphocyte count (ALC) ≥ 750/µL;
- Hemoglobin ≥ 9 g/dL.

Subject History

- 7. Subjects are 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.
- 8. Subjects must not have a history of clinically significant (per investigator judgment) drug or alcohol abuse within the last 6 months. *(Note: Do not perform urine drug screen at Baseline Visit).*
- 9. Subjects must have no current or past history of the following:
  - Two or more episodes of herpes zoster, or one or more episodes of disseminated herpes zoster;
  - One or more episodes of disseminated herpes simplex (including eczema herpeticum/Kaposi varicelliform eruption);
  - Human immunodeficiency virus (HIV) infection, defined as confirmed positive anti-HIV antibody (HIV Ab) test;
  - Active tuberculosis (TB) or meet TB exclusionary parameters (specific requirements for TB testing are provided in the operations manual);
  - Positive result of beta-D-glucan (screening for pneumocystis jirovecii infection) or 2 consecutive indeterminate results of beta-D-glucan during the Screening Period (for subjects in Japan only);
  - Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular (IM) anti-infectives within 14 days prior to the Baseline Visit;
  - Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
  - Confirmed COVID-19: The Baseline Visit must be at least 14 days from onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement in symptoms;

- Suspected COVID-19: Subjects with signs/symptoms suggestive of COVID-19, known exposure, or high risk behavior should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure.

10. Subjects must not have evidence of:

- Hepatitis B virus (HBV): hepatitis B surface antigen positive (+) test or detectable HBV DNA PCR qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+)(and for hepatitis B surface antibody [HBs Ab] positive [+] subjects where mandated by local requirements);
- Hepatitis C virus (HCV): detectable HCV RNA in any subject with anti-HCV Ab.

11. Subjects must not have any of the following medical diseases or disorders:

- Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting, and aorto-coronary bypass surgery;
- History of an organ transplant which requires continued immunosuppression;
- History of GI perforation (other than due to appendicitis or mechanical injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment;
- Conditions that could interfere with drug absorption including but not limited to short bowel syndrome or gastric bypass surgery; subjects with a history of gastric banding/segmentation are not excluded;
- History of malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix;
- Uncontrolled thyroid disease;
- Other skin conditions that would interfere with evaluation of vitiligo;
- > 33% leukotrichia on the face or > 33% leukotrichia on the body (including face).

12. There must be no reason the investigator believes that the subject is an unsuitable candidate to participate in the study, receive study drug, or would be placed at risk by participating in the study.

Contraception

13. For all females of child-bearing potential: must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at Baseline prior to the first dose of study drug (local practices may require serum pregnancy testing at Baseline). Subjects with a borderline serum pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological causes of borderline results and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).

- 14. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from Study Day 1 through at least 30 days after the last dose of study drug (local practices may require 2 methods of birth control) (refer to Section 5.2 for more details on contraception). Female subjects of non-childbearing potential do not need to use birth control.
- 15. Female must not be **pregnant, or breastfeeding, and is not considering becoming pregnant or donating eggs** during the study and for 30 days after the last dose of study drug.

Prior and Concomitant Medications and Therapies

- 16. Subjects must not have previously been treated with any topical or systemic JAK inhibitor.
- 17. Subjects must not have previously been treated with any permanent skin bleaching agents to treat vitiligo.
- 18. Subjects must not have been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study or was previously enrolled in this study.
- 19. Subjects who have had prior exposure to immunomodulatory biologic therapy, for any indications, must have discontinued the biologic therapy prior to the first dose of study drug. Recommended washout periods are specified below. If not specified below, biologic therapies must be discontinued at least 5 times the mean terminal elimination half-life of a drug or 3 months prior to Baseline, whichever is longer.
  - ≥ 4 weeks for etanercept;
  - ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and ixekizumab;
  - ≥ 16 weeks for secukinumab;
  - ≥ 12 weeks for ustekinumab.
- 20. Subjects must not have been treated with any systemic vitiligo therapy (e.g., methotrexate [MTX], mycophenolate mofetil, corticosteroids) or supplemental vitiligo therapy (antioxidants/vitamins/herbal medicine/traditional Chinese medicine) within a minimum of 30 days prior to the first dose of study drug.
- 21. Subjects must not have been treated with any topical vitiligo therapy including permanent and temporary tattoos within a minimum of 30 days prior to the first dose of study drug. (Note: Camouflage and makeup may be used).
- 22. Subjects must not have been treated with any phototherapy, including excimer (or other forms of laser therapy), within a minimum of 12 weeks prior to the first dose of study drug.

- 23. Subjects must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from Screening through the end of study drug administration or strong CYP3A inducers 30 days prior to study drug administration through the end of study drug administration (refer to Table 1 in Section 5.3 for examples of commonly used strong CYP3A inhibitors and inducers). Subjects may not use herbal therapies or other traditional medicines with unknown effects on CYP3A from Screening through the end of study drug administration.
- 24. Subjects must not have received a live vaccine within 28 days (or longer if required locally) prior to the first dose of study drug, or have expected need of live vaccination during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.
- 25. Subjects 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.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

Females, Non-Childbearing Potential

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

1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
   - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.
   - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
2. Postmenopausal female
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

Females of Childbearing Potential

Review and document pregnancy avoidance recommendations with females of childbearing potential.

Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days after the last dose of study drug. Females must commit to one of the following methods of highly effective birth control:

- Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure) (For Japan: only bilateral tubal ligation).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner (the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence (unless not acceptable per local practices), defined as: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, females of childbearing potential must commit to using 2 methods of contraception (either 2 highly effective methods or 1 highly effective method combined with 1 effective method). Effective methods of birth control are the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Baseline Day 1.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with a cap, diaphragm, or sponge with spermicide (double barrier method).

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

5.3 Prohibited Medications and Therapy

Corticosteroids

Systemic corticosteroids for treatment of vitiligo including, but not limited to, oral, intravenous, IM, and intralesional are prohibited throughout the study. For non-vitiligo reasons, use of systemic corticosteroids can be used but limited to prednisone or prednisolone for up to 1 mg/kg/day for no more than 2 consecutive weeks; any subject who receives systemic corticosteroids for more than 2 consecutive weeks, regardless of the dosage of corticosteroid, should permanently discontinue study drug.

Topical Therapy

Topical treatments for vitiligo (including, but not limited to topical calcineurin inhibitors, topical corticosteroids, topical prostaglandin analogs) are prohibited until after Week 24 Visit assessments. Subjects are not permitted to receive permanent or temporary tattoos within 30 days prior to the first dose of study drug through the end of the study.

Phototherapy, Tanning Booth, Extended Sun Exposure, and Surgical Grafting

Phototherapy (including, but not limited to, broadband UV-B, narrowband UV-B, psoralen and UV-A, excimer or other laser therapy, tanning booth use) is prohibited for at least 12 weeks prior to the Baseline Visit and prohibited during the study. However, subjects are allowed to receive natural daily light following a normal routine, but, for a prolonged exposure to sunlight, sunscreen is recommended. Surgical grafting for vitiligo is not allowed during the study.

Supplemental Vitiligo Therapy Including Over the Counter (Antioxidants/Vitamins/Herbal Medicine/Traditional Chinese Medicine)

Supplemental therapy for vitiligo (including, but not limited to, antioxidants, vitamins, herbal supplements, traditional Chinese medicine) is not permitted until after Week 24 Visit assessments. However, for any drugs that are considered strong CYP3A inhibitors or inducers, or any herbal supplements or traditional medicines with unknown effects on CYP3A are prohibited throughout the entire the study. Subjects must have discontinued supplemental therapies at least 30 days prior to the first dose of study drug.

JAK Inhibitors

Prior and concomitant oral and topical exposure to any other JAK inhibitors besides the investigational drug, upadacitinib, in this study (including but not limited to ruxolitinib [Jakafi®], tofacitinib [Xeljanz®], baricitinib [Olumiant®], abrocitinib [PF-04965842], and filgotinib) is not allowed.

Targeted Biologic Therapies

Subjects must have discontinued immunomodulatory biologic therapies prior to the first dose of study drug as specified in the washout procedures (Eligibility Criterion 19, Protocol Section 5.1). No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented.

Current and concomitant biologic therapies and biosimilar versions of biologic drugs are prohibited during the study. Examples of biologic therapies include, but are not limited to, the following:

- Humira® (adalimumab)
- Dupixent® (dupilumab)
- Zolair® (omalizumab)
- Enbrel® (etanercept)
- Remicade® (infliximab)
- Orencia® (abatacept)

- Kineret® (anakinra)
- Rituxan® (rituximab)
- Cimzia® (certolizumab pegol)
- Simponi® (golimumab)
- Actemra® (tocilizumab)
- Raptiva® (efalizumab)
- Tysabri® (natalizumab)
- Stelara® (ustekinumab)
- Benlysta® (belimumab)
- Taltz® (ixekizumab)
- Cosentyx® (secukinumab)
- Tremfya® (guselkumab)
- SKYRIZI® (risankizumab) or SKYRIZI® (risankizumab-rzaa)

Other Non-Biologic Systemic Therapy

Other systemic therapy for the treatment of vitiligo is prohibited during the study including, but not limited to:

- MTX
- cyclosporine
- azathioprine
- phosphodiesterase type 4 -inhibitors (e.g., apremilast)
- mycophenolate mofetil

Investigational Drugs

Subjects who have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in this study. Investigational drugs are also prohibited during the study.

Vaccines

Live vaccines are prohibited during study participation and including at least 30 days (or longer if required locally) after the last dose of study drug. If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed at least 28 days (or longer if required locally) before first dose of study drug with appropriate precautions. Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. Examples of live vaccines include, but are not limited to, the following:

- Monovalent live attenuated influenza A (H1N1) (intranasal)
- Seasonal trivalent live attenuated influenza (intranasal)
- Zostavax (herpes zoster, live attenuated)
- Rotavirus
- Varicella (chicken pox)
- Measles-mumps-rubella or measles-mumps-rubella-varicella
- Oral polio vaccine
- Smallpox
- Yellow fever
- Bacille Calmette-Guérin
- Typhoid (oral)

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

COVID-19 Vaccine

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.

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors (includes over-the-counter or prescription medicines, vitamins, and/or herbal supplements) is not permitted from Screening through the end of study drug administration and use of strong CYP3A inducers is not permitted from 30 days prior to study drug administration through the end of study drug administration. Table 1 includes examples of commonly used strong CYP3A inhibitors and inducers. 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.

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

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

Elective and Emergency Surgeries:

Elective surgery will not be allowed during the study until the primary endpoint has been assessed (Week 24). If the subject undergoes elective surgery, the study drug should be interrupted 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.

If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency 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.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of 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 on the appropriate electronic case report form (eCRF). Also, medications taken for vitiligo 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, and route of administration.

5.5 Withdrawal of Subjects and Discontinuation of Study

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 deriving 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.

Subjects can request to be discontinued from participating in the study at any time for any reason. The investigator may discontinue any subject's participation at any time for any reason. The AbbVie Therapeutic Area Medical Director (TA MD)/Scientific Director may mandate individual subject discontinuation from study drug in case of safety concern.

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

- The subject requests withdrawal from study drug or the study.
- The investigator believes it is in the best interest of the subject.
- Abnormal laboratory results or AEs that either meet the criteria for discontinuation of study drug, as stated in Section 6.2, or rule out safe continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Serious infections (e.g., sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk with continuation of the study drug.
- Confirmed diagnosis of DVT, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Subject develops a malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject develops a GI perforation (defined as acute, spontaneous perforation of the GI tract that requires inpatient medical care or urgent surgical intervention other than appendicitis or mechanical injury). See also Section 6.2 Toxicity Management.
- The subject becomes pregnant or plans to become pregnant while on study drug.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk. Note: intentional/prospective deviations from the protocol are NOT allowed, see Section 5.9 Protocol Deviations.

- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- Subject is significantly non-compliant with study procedures.
- Worsening vitiligo as defined by an increase of 25% or higher in T-VASI from Baseline beginning at Week 8.

Additional requirements related to abnormal laboratory values and selected AESIs are located in Section 6.2.

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation

If a subject prematurely discontinues study drug, the procedures outlined for the Premature Discontinuation (PD) Visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation, and preferably prior to initiation of another therapy. In addition, a 30-day Follow-up Visit or phone call should occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

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

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

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

5.7 Study Drug

Study drug will be taken orally QD, 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.

AbbVie will not supply any vitiligo disease-related concomitant medication therapy taken during the course of the study. AbbVie will supply upadacitinib and matching upadacitinib placebo.

Study drug will be packaged in quantities sufficient to accommodate the study design.

Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. 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 the study.

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug

Investigational Product	Mode of Administration	Dosage Form	Strength	Blinded or Open Label	Frequency	Manufacturer
Upadacitinib (ABT-494)	Oral	Extended-release, film-coated tablets	6 mg, 11 mg, or 22 mg	Blinded	QD	AbbVie
Placebo for upadacitinib (ABT-494)	Oral	Film-coated tablets	Not applicable	Blinded	QD	AbbVie

During the COVID-19 pandemic, study drug shipment can be made from the study site to the subject if allowed by local regulations. Refer to the operations manual for details on direct-to-patient shipment of study drug.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule. Subjects who meet eligibility criteria at Baseline will be randomized in a 2:2:2:1:1 ratio to one of the five treatment groups:

- Group 1: upadacitinib 22 mg QD (N = 40) (Period 1) → upadacitinib 22 mg QD (Period 2)
- Group 2: upadacitinib 11 mg QD (N = 40) (Period 1) → upadacitinib 11mg QD (Period 2)
- Group 3: upadacitinib 6 mg QD (N = 40) (Period 1) → upadacitinib 6 mg QD (Period 2)
- Group 4: placebo (N = 20) (Period 1) → upadacitinib 22 mg QD (Period 2)
- Group 5: placebo (N = 20) (Period 1) → upadacitinib 11 mg QD (Period 2)

Randomization will be stratified by the age group (≤ 50 and > 50), Baseline disease severity (T-VASI < 15 and ≥ 15), and status of active vitiligo (Yes/No) defined as follows:

- Active: Showing new lesions or progression (enlargement) of existing lesions within the last 6 months and/or presenting clinical subtypes indicative of progressing vitiligo (i.e., confetti-like depigmentation, trichrome pattern, or Koebner phenomenon).

At Week 24, subjects who were randomized to placebo at Baseline will be switched to either 22 mg (Group 4) or 11 mg (Group 5) upadacitinib in a blinded fashion per pre-specified randomization assignments.

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 Week 24 primary analysis for the study, while the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the upadacitinib tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

In the event of a medical emergency that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the 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/helpdesk/.

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.

5.9 Protocol Deviations

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

In Japan, the investigator will record all protocol deviations in the appropriate medical records at the site.

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, device damage or not working properly, or packaging issues.

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

Medical Complaints/Adverse Events and Serious Adverse Events

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

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

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

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly

during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 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 (ADL) 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 or 5 half-lives, whichever is longer, after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs):

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

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

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

Adverse Events of Special Interest

The following AESIs will be monitored during each study:

- Serious infections
- Opportunistic infections (excluding TB and herpes zoster)
- Herpes Zoster
- Active TB
- Adjudicated GI perforations
- Malignancy (all types)
- Anemia
- Neutropenia
- Lymphopenia
- Renal dysfunction
- Hepatic disorders
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event)
- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system)

Cardiovascular Adjudication Committee

An independent, external committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular, cerebrovascular, embolic, and thrombotic AEs in a blinded manner as defined by the CAC charter. The CAC charter will be prepared separate from the protocol and will describe the objective, scope, frequency, and triggers for data reviews.

GI Perforation Adjudication

Two independent, blinded internal adjudicators along with a third potential tie-breaker adjudicator who are gastroenterologists or who have other highly relevant clinical experience will be utilized to assess potential AEs of acute spontaneous GI perforation.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE version 5.0, which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications.

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

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
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 refers 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 use the following definitions to assess the relationship of the AE to the use of study drug:

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

Pregnancy

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

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. 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 from study drug treatment (Protocol Section 5.5).

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an 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 AESIs, consists of safety monitoring (review of AEs on an ongoing basis, and periodic/ad hoc review of safety issues by an independent DMC), 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.

Serious Infections: Study drug should be interrupted if a subject develops a serious infection. 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.

GI Perforation: Subjects presenting with the onset of signs or symptoms of a GI perforation should be evaluated promptly for early diagnosis and treatment. Subjects with acute, spontaneous perforation of the GI tract that requires inpatient medical care or urgent surgical intervention (except for appendicitis or mechanical injury) must be permanently discontinued from 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 confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at increased risk for skin cancer.

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 treating physician.

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

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. 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 is to occur as soon as possible. Further, repeat testing may be performed at a local laboratory if the subject is unable to use the central laboratory.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL, interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline and an alternative etiology is known 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 normal reference range or its Baseline value.
ANC	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Interrupt study drug if confirmed < 500/µL by repeat testing with new sample. If value returns to normal reference range or its Baseline value, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason that rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
ALC	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total WBC count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until WBC count returns to normal reference range or its Baseline value.

Laboratory Parameter	Toxicity Management Guideline

AST or ALT	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5.
	  • A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from Baseline).
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD.
	Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA 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) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or the Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.
	For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

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 restart study drug once serum creatinine returns to ≤ 1.5 × Baseline value and ≤ ULN. For the above serum creatinine elevation scenarios, complete the supplemental renal eCRF.

6.3 Independent Data Monitoring Committee

To ensure subject safety, an external, independent DMC will review unblinded safety data on a cohort level, at approximately 4-month intervals throughout the course of the study, and alert AbbVie to possible safety concerns related to the conduct of the study. The DMC will review safety data to determine if there are any significant safety concerns that would warrant any study action. If necessary to assess benefit/risk, the DMC will also be given access to selected efficacy data.

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.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

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

The primary analysis will be conducted after all subjects have completed Week 24, data pertaining to Period 1 have been cleaned, and a database lock has occurred for the purpose of efficacy and safety analysis in Period 1. The efficacy analysis performed based on this database lock will be the only and final analysis for Period 1.

7.2 Definition for Analysis Populations

The ITT Population includes all randomized subjects. Subjects will be included in the analysis based on treatment as randomized. The ITT Population will be used for all efficacy analyses.

The following populations will be used for the safety analysis:

- The Safety Population (Safety) is defined as all subjects who are randomized and received at least 1 dose of study drug in the study.
- The all upadacitinib treated (ALL_UPA) Population is defined as all subjects who received at least 1 dose of upadacitinib in the study. This population will be used to provide a comprehensive summary of safety.

7.3 Handling Potential Intercurrent Events for the Primary Endpoint

The primary endpoint (Section 3.2) will be analyzed in the ITT Population and no intercurrent events will be considered. All data collected, regardless of premature discontinuation of study drug, will be used in the analysis.

7.4 Statistical Analyses for Efficacy

The efficacy analysis will be based on the ITT Population and all statistical tests will be performed at a 2-sided significance level of 0.1. The 95% confidence interval of the treatment effect will be provided.

- For continuous variables, comparisons of change and/or percent change from Baseline will be made between upadacitinib and placebo based on the Mixed Model Repeated Measures (MMRM) adjusting for treatment, visit, treatment-by-visit interaction, and stratification factors derived by the actual value (age group [≤ 50 and > 50], Baseline disease severity [T-VASI < 15 and ≥ 15], and status of active vitiligo [Yes/No]) as fixed factors, and Baseline value as a covariate. The MMRM will be the primary approach to handle missing values for continuous endpoints.
- For categorical variables, comparisons will be made between upadacitinib and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factors derived by the actual value: age group (≤ 50 and > 50), Baseline disease severity (T-VASI < 15 and ≥ 15), and status of active vitiligo (Yes/No). Non-Responder Imputation incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-MI) will be the primary approach to handle missing values for categorical endpoints.

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint will be conducted on the ITT Population based on the treatment as randomized. Comparison of the primary endpoint will be made between each upadacitinib dose and placebo using the MMRM adjusting for treatment, visit, treatment-by-visit interaction, stratification factors derived by the actual value, and Baseline value at a 2-sided significance level of 0.1.

MMRM will be the primary approach to handle missing values. A sensitivity analysis will also be performed for the primary efficacy endpoint, using MI to handle missing values. Analysis details for MMRM, MI, and other sensitivity analyses (if applicable) will be provided in the SAP.

Summary and Analysis of Secondary Endpoints

Analysis of secondary efficacy endpoints will be conducted on the ITT Population based on the treatment as randomized. The continuous endpoints will be analyzed using the same method as for the primary endpoint. The categorical endpoints will be analyzed using the CMH test. The null hypotheses for all secondary endpoints will be tested at a 2-sided significance level of 0.1.

Summary and Analysis of Additional Efficacy Endpoints

Additional endpoints, as described in Section 3.4, will also be analyzed. Analysis details will be provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the consistency of the efficacy across demographic and other Baseline characteristics, summaries and analyses will be performed for selected subgroups for the primary efficacy endpoint. The subgroups will be defined in SAP.

7.5 Statistical Analyses for Safety

All safety analyses will be performed for the Safety Population and ALL_UPA Population. Subjects will be analyzed based on the treatment actually received. The number and percentage of subjects experiencing AEs will be tabulated using Medical Dictionary for Regulatory Activities system organ class and preferred term, as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient-years) of SAEs, deaths, and AEs leading to discontinuation will be provided as well.

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

7.6 Interim Analysis

No formal interim analysis of efficacy is planned for this study. Routine safety reviews will be performed by an external independent DMC (see details in Section 6.3).

7.7 Overall Type I Error Control

Multiplicity from multiple comparisons will not be adjusted in this Phase 2 study.

7.8 Sample Size Determination

Assuming a Week 24 percent change from Baseline in F-VASI of 0% in the placebo arm, a conservative estimate based on a prior study in vitiligo,[14] the planned total sample size of 160 subjects (40 subjects in each upadacitinib group, 40 subjects total in the placebo groups) will provide more than 90% power to detect the treatment difference of 40% reduction (assuming a standard deviation of 54.8%) in at least 1 upadacitinib group versus placebo using a 2-sided significance level of 0.1 based on the two-sample t-test.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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

8.2 Ethical Conduct of the Study

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

In cases of COVID-19 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., 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.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

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

12 REFERENCES

1. Oiso N, Suzuki T, Fukai K, et al. Nonsegmental vitiligo and autoimmune mechanism. Dermatol Res Pract. 2011;2011:518090.

2. Morrison B, Burden-Teh E, Batchelor JM, et al. Quality of life in people with vitiligo: a systematic review and meta-analysis. Br J Dermatol. 2017;177(6):e338-e9.

3. Alikhan A, Felsten LM, Daly M, et al. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011;65(3):473-91.

4. Ezzedine K, Lim HW, Suzuki T, et al. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res. 2012;25(3):E1-13.

5. Patel KR, Singam V, Rastogi S, et al. Association of vitiligo with hospitalization for mental health disorders in US adults. J Eur Acad Dermatol Venereol. 2019;33(1):191-7.

6. Sheth VM, Guo Y, Qureshi AA. Comorbidities associated with vitiligo: a ten-year retrospective study. Dermatology. 2013;227(4):311-5.

7. Elbuluk N, Ezzedine K. Quality of Life, Burden of Disease, Co-morbidities, and Systemic Effects in Vitiligo Patients. Dermatol Clin. 2017;35(2):117-28.

8. Dahir AM, Thomsen SF. Comorbidities in vitiligo: comprehensive review. Int J Dermatol. 2018;57(10):1157-64.

9. Teulings HE, Overkamp M, Ceylan E, et al. Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. Br J Dermatol. 2013;168(1):162-71.

10. Rodrigues M. Skin Cancer Risk (Nonmelanoma Skin Cancers/Melanoma) in Vitiligo Patients. Dermatol Clin. 2017;35(2):129-34.

11. Rodrigues M, Ezzedine K, Hamzavi I, et al. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol. 2017;77(1):1-13.

12. Harris JE, Harris TH, Weninger W, et al. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-γ for autoreactive $CD8^+$ T-cell accumulation in the skin. J Invest Dermatol. 2012;132(7):1869-76.

13. Relke N, Gooderham M. The Use of Janus Kinase Inhibitors in Vitiligo: A Review of the Literature. J Cutan Med Surg. 2019;23(3):298-306.

14. Rosmarin D, Pandya AG, Lebwohl M, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. Lancet. 2020;396(10244):110-20.

15. Incyte. Topical Ruxolitinib Evaluation in Vitiligo Study 1 (TRuE-V1), CT.gov Identifier: NCT04052425. Bethesda, MD: US National Library of Medicine; Mar 2020 [cited 2020 Sep 08]. Available from: https://clinicaltrials.gov/ct2/show/NCT04052425.

16. Incyte. Topical Ruxolitinib Evaluation in Vitiligo Study 2 (TRuE-V2), CT.gov Identifier: NCT04057573. Bethesda, MD: US National Library of Medicine; Mar 2020 [cited 2020 Sep 08]. Available from: https://clinicaltrials.gov/ct2/show/NCT04057573.

17. Nicolaidou E, Antoniou C, Stratigos AJ, et al. Efficacy, predictors of response, and long-term follow-up in patients with vitiligo treated with narrowband UVB phototherapy. J Am Acad Dermatol. 2007;56(2):274-8.

18. Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145(3):877-84.

19. AbbVie. Upadacitinib Investigator's Brochure Edition 11. 18 August 2020.

20. Kim SR, Heaton H, Liu LY, et al. Rapid Repigmentation of Vitiligo Using Tofacitinib Plus Low-Dose, Narrowband UV-B Phototherapy. JAMA Dermatol. 2018;154(3):370-1.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	antibody
AD	atopic dermatitis
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALL_UPA	all upadacitinib treated
ALT	alanine transaminase
ANC	absolute neutrophil count
AS	ankylosing spondylitis
AST	aspartate transaminase
BSA	body surface area
CAC	Cardiovascular Adjudication Committee
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form
CRP	C-reactive protein
CXR	chest x-ray
CYP3A	cytochrome P450 3A
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTP	direct-to-patient
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
F-PaGVA	Face – Patient Global Vitiligo Assessment
F-PhGVA	Face – Physician Global Vitiligo Assessment
FSH	follicle-stimulating hormone

F-VASI	Facial Vitiligo Area Scoring Index
GCP	Good Clinical Practice
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HBc Ab	hepatitis B core antibody
HBs Ab	hepatitis B surface antibody
HBs Ag	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV Ab	human immunodeficiency virus antibody
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICVA	Individual Component Vitiligo Assessment
IEC	Independent Ethics Committee
IFN	interferon
IM	intramuscular
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-Treat
IU	International Unit
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed Model Repeated Measures
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMSC	non-melanoma skin cancer
NSV	non-segmental vitiligo
PaGIC-V	Patient's Global Impression of Change-Vitiligo
PBMC	peripheral blood mononuclear cells

PCR	polymerase chain reaction
PD	Premature Discontinuation
PhGIC-V	Physician's Global Impression of Change-Vitiligo
PhGVA	Physician Global Vitiligo Assessment
PK	pharmacokinetic
PPD	purified protein derivative (tuberculin)
PRO	patient-reported outcome
PsA	psoriatic arthritis
PT	preferred term
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	system organ class
STAT	Signal Transducers and Activators of Transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TEAE	treatment-emergent adverse event
T-PaGVA	Total – Patient Global Vitiligo Assessment
T-PhGVA	Total – Physician Global Vitiligo Assessment
TPO	thyroid peroxidase
TSH	thyroid-stimulating hormone
T-VASI	total Vitiligo Area Scoring Index
T4	thyroxine
ULN	upper limit of normal
UV	ultraviolet
VASI	Vitiligo Area Scoring Index
VES	vitiligo extent score
VitiQoL	vitiligo quality-of-life

VNS	vitiligo noticeability scale
WBC	white blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-051: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Non-Segmental Vitiligo

Protocol Date: 07 July 2021

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager II	Clinical Program Development
	Program Lead II	Clinical Program Development
	Senior Medical Writer	Medical Writing
	Senior Scientific Director	Immunology Clinical Development
	Director	Data and Statistical Sciences
	Senior Director & Statistics Therapeutic Area Head	Data and Statistical Sciences
	Director	Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across Screening and subsequent study visits. The individual activities are described in detail in the operations manual (Appendix F). Allowed modifications due to the COVID-19 pandemic are detailed within the operations manual.

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Study Activities Table

Activity	Screening	Period 1							Period 2				PD Visit	30-Day Follow-up Visit/Call
	Day –35 to Day –1	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8 Day 57	Week 12 Day 85	Week 18 Day 127	Week 24 Day 169	Week 28 Day 197	Week 36 Day 253	Week 44 Day 309	Week 52 Day 365		
Visit Window			± 3 Days						± 7 Days					
INTERVIEWS & QUESTIONNAIRES														
Informed consent	✓													
Eligibility criteria	✓	✓												
Medical/surgical history	✓	✓												
Alcohol and nicotine use	✓													
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB risk assessment questionnaire	✓													
Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-Reported Outcome														
VitiQoL, HADS		✓				✓		✓		✓		✓	✓	
F-PaGVA, T-PaGVA		✓		✓	✓	✓		✓		✓		✓	✓	
DLQI		✓						✓				✓	✓	
VNS, PaGIC-V				✓	✓	✓		✓		✓		✓	✓	

Activity	Screening	Period 1							Period 2				PD Visit	30-Day Follow-up Visit/Call
	Day –35 to Day –1	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8 Day 57	Week 12 Day 85	Week 18 Day 127	Week 24 Day 169	Week 28 Day 197	Week 36 Day 253	Week 44 Day 309	Week 52 Day 365		
Visit Window			± 3 Days						± 7 Days					
EXAMS														
Physician Assessments: vitiligo history form	✓													
Physician Assessments: F-VASI, T-VASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physician Assessments: VES		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physician Assessments: PhGIC-V				✓	✓	✓		✓		✓		✓	✓	
Physician Assessments: F-PhGVA, T-PhGVA		✓		✓	✓	✓		✓		✓		✓	✓	
Physician/Patient Assessments: ICVA		✓						✓				✓	✓	
CXR	✓													
12-lead ECG	✓											✓	✓	
Height	✓													
Weight	✓	✓				✓		✓				✓	✓	
Vital signs (blood pressure, heart rate, respiratory rate, body temperature)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination including skin examination	✓	✓						✓				✓	✓	
Digital Imaging (performed only at a subset of sites)		✓		✓		✓		✓		✓		✓		
LOCAL LAB														
Urine pregnancy test (at Baseline, Week 2, Week 4, and every 4 weeks thereafter)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Activity	Screening	Period 1							Period 2				PD Visit	30-Day Follow-up Visit/Call
	Day –35 to Day –1	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8 Day 57	Week 12 Day 85	Week 18 Day 127	Week 24 Day 169	Week 28 Day 197	Week 36 Day 253	Week 44 Day 309	Week 52 Day 365		
Visit Window			± 3 Days						± 7 Days					
CENTRAL LAB														
HCV/HIV Ab (unless prohibited by local regulators) screening	✓													
HBV screening (post-Baseline tests for subjects from Japan only)	✓					✓		✓		✓	✓		✓	
Serum pregnancy test	✓													
FSH (if applicable)	✓													
QuantiFERON-TB Gold test (and/or local purified protein derivative [tuberculin] skin test)	✓													
High-sensitivity C-reactive protein (will remain blinded throughout the trial)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Hematology (complete blood count) and clinical chemistry (lipid panel at Screening, Baseline, Week 12, Week 24, Week 36, and Week 52 only)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urinalysis	✓	✓				✓		✓		✓		✓		
Thyroid-stimulating hormone, thyroxine (T4), and anti-thyroid peroxidase	✓													
Beta-D-glucan (Japan only)	✓													
Blood samples for upadacitinib PK assay		✓		✓	✓	✓		✓					✓	
Optional biomarker samples: whole blood DNA		✓												
Optional biomarker samples: whole blood RNA		✓		✓				✓						
Optional biomarker samples: serum/plasma proteomic		✓	✓	✓		✓		✓	✓			✓		
Optional biomarker samples: CD8+ phenotyping		✓	✓	✓		✓		✓	✓			✓		
Optional biomarker samples: peripheral blood mononuclear cells		✓		✓				✓						

Activity	Screening	Period 1							Period 2				PD Visit	30-Day Follow-up Visit/Call
	Day –35 to Day –1	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8 Day 57	Week 12 Day 85	Week 18 Day 127	Week 24 Day 169	Week 28 Day 197	Week 36 Day 253	Week 44 Day 309	Week 52 Day 365		
Visit Window			± 3 Days						± 7 Days					
Optional biomarker samples: lesional skin biopsy		✓		✓				✓						
Optional biomarker samples: non-lesional skin biopsy		✓						✓						
℞ TREATMENT														
Randomization/drug assignment		✓												
Dispense study drug & subject dosing diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Review and copy subject dosing diary and perform drug reconciliation			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	15 March 2021

The purpose of this version is to address the following changes in addition to minor clerical corrections for consistency throughout:

Protocol

- Update Title Page to change sponsor/emergency medical contact from [redacted] MD, MS, DVM, FAAD to [redacted] MD, PhD, and to update contact information accordingly.

  Rationale: *To update due to personnel change.*

- Update Synopsis and Section 2.1 to add "in some countries" to clarify the approval status of upadacitinib for the treatment of RA, PsA, and AS.

  Rationale: *To align with indication approvals outlined in the investigator brochure. According to the current IB, upadacitinib is approved for RA and is being evaluated for other indications.*

- Update Synopsis and Section 5.1 eligibility criterion #17 to indicate that subjects must not have been previously treated with any permanent skin bleaching agents to treat vitiligo.

  Rationale: *To clarify that previous treatment with permanent skin bleaching agents to treat vitiligo is prohibited.*

- Update Section 3.8 to add wording for site and subject participation in the Digital Imaging Research.

  Rationale: *To clarify the approximate number of sites that will be selected and that subjects at participating sites will be required to participate after digital imaging platform is available for implementation at the site.*

- Update Section 5.3 to revise the dose for systemic corticosteroids from 1 mg/kg to 1 mg/kg/day.

  Rationale: *To provide the correction needed regarding the maximum dose of systemic corticosteroids allowed.*

- Update Section 5.3 to change the wording regarding natural daily light exposure from "encouraged" to "allowed."

  Rationale: *To provide clarification.*

- Update Section 5.3 to add language prohibiting use throughout the study of any drugs considered to be strong CYP3A inhibitors or inducers, or herbal supplements or traditional medicines with unknown effects on CYP3A.

  Rationale: *To provide additional language as topical and supplemental treatments may interfere with upadacitinib metabolism and exposure and may also impact efficacy and safety of upadacitinib treatment.*

- Update to Targeted Biologic Therapies in Section 5.3 to include the U.S. marketed product name and to update to the registered trademark for EU SKYRIZI.

  Rationale: *To provide clarification.*

- Update Section 5.5 to add the following language in the event that an eligibility criteria violation was noted after the subject started study drug and continuation of study drug would place the subject at risk: "Note: indicate that intentional/prospective deviations from the protocol are not permitted."

  Rationale: *To provide clarification in response to a request from Health Canada.*

- Update Section 5.5 to condense the wording regarding subject non-compliance with study procedures.

  Rationale: *To simplify the wording as significant non-compliance with study procedures would be sufficient cause to consider discontinuation for a clinical trial, regardless of the perceived risk to the subject. Also, significant non-compliance has the potential to have a negative impact on the scientific integrity of the study.*

- Update Section 5.5 to add "beginning at Week 8" to the discontinuation criterion regarding worsening vitiligo as defined by an increase of 25% or higher in T-VASI from Baseline.

  Rationale: *To clarify that subjects with 25% increase in T-VASI will not be discontinued until Week 8 to allow sufficient time for upadacitinib to show some improvement, thus minimizing early premature discontinuation.*

- Update Section 7.4 to clarify that categorical stratification factors will be adjusted in the models.

  Rationale: *to clarify that categorical stratification factors are adjusted in the models instead of the continuous values of the variables.*

- Update Appendix A to add abbreviations.

  Rationale: *To keep abbreviations list current.*

- Update Appendix C to revise List of Protocol Signatories.

  Rationale: *To update protocol signatories to reflect current personnel.*

- Update Appendix D to add respiratory rate and body temperature to vital signs.

  Rationale: *To provide consistency for vital signs in Operations Manual Section 3.14 where vital signs are defined as "systolic and diastolic blood pressure in sitting position, heart rate, respiratory rate, and body temperature," and in Appendix D, Activity Schedule.*

Operations Manual

- Update Section 1 and Section 4.3 to change sponsor/emergency medical contact from [redacted] MD, MS, DVM, FAAD to [redacted] MD, PhD, and to update contact information accordingly.

  Rationale: *To update due to personnel change.*

- Update Section 2.1 Baseline/Day 1 to add a footnote indicating that study drug dispensed at Baseline contains 35 tablets; therefore, study drug will not be dispensed from IRT at Week 2.

Rationale: *To provide clarification that no study drug dispensation from the IRT system will occur at the Week 2 visit.*

- Update Section 2.1 Week 2/Day 15 to add a footnote that study drug dispensation from IRT at Baseline will be reviewed for compliance and returned to subject at this visit. IRT dispensation at this visit is not available.

  Rationale: *To clarify that no study drug dispensation from the IRT system will occur at the Week 2 visit.*

- Update Section 2.1 Week 12/Day 85, Week 24/Day 169, Week 36/Day 253, Week 44/Day 309, and Premature Discontinuation Visit to add the following footnote regarding HBV post-Baseline tests for subjects from Japan only: HBV DNA PCR testing approximately every 12 weeks is not necessary when the subject has a history of HBV vaccination and HBs Ab+ and HBc Ab–. If necessary, HBV DNA PCR may be tested at unscheduled visits.

  Rationale: *To clarify when additional testing is required.*

- Update Section 3.3 to add language that additional temporary verbal consent may be obtained in accordance with local regulations, followed by an appropriately signed and dated informed consent form obtained from the subject afterwards, as soon as possible.

  Rationale: *To provide updated guidance on informed consent from subjects due to protocol modifications that may become necessary during the COVID-19 pandemic.*

- Update Section 3.7 to clarify the description of the VNS and VitiQoL.

  Rationale: *To provide clarification.*

- Update Section 3.7 to correct the response option ranges from 0 = no depigmentation to 4 = very extensive pigmentation.

  Rationale: *To provide correction for T-PaGVA and F-PaGVA scale response options.*

- Update Section 3.8 to add language regarding how the VES will initially be collected and how the final score will be calculated before upload into EDC by the site.

  Rationale: *To clarify the steps necessary to collect the VES based on the way it was initially validated.*

- Update Section 3.9 to replace the level of bother response option of "not applicable" to "area not affected by vitiligo."

  Rationale: *To clarify how some of the ICVA data is collected into EDC.*

- Update Section 3.11 to state that PK samples should be collected at 0.5 to 4 hours post-dosing at Baseline and Week 4. At Weeks 8, 12, and 24, subjects should take the study drug dose at the clinic within 30 minutes after collecting the PK blood sample.

  Rationale: *To add PK collection timepoint for Baseline and a 30-minute window for taking study drug dose after PK sample collection at Weeks 8, 12, and 24.*

- Update Section 3.11 to indicate that data and accurate time of dose administration will be recorded in the eCRF for doses administered at the clinic during a study visit.

  Rationale: *To provide additional clarification regarding data and accurate time capture of study drug dose administration.*

- Update Section 3.13 to indicate that body weight will be measured at scheduled visits as specified in Section 2.1 and in Appendix D, Activity Schedule.

  Rationale: *To clarify weight collection timepoints.*

- Update Section 3.14 to change "pulse rate" to "heart rate."

  Rationale: *To provide consistency with wording in Section 3.14 and Appendix D, Activity Schedule.*

- Update Section 3.18 to remove the following sentence: "AbbVie will not receive results from the testing and will not be made aware of any positive result."

  Rationale: *Although AbbVie does not require receiving HIV test results, AbbVie CRAs are required to verify all study eligibility criteria, including the lack of confirmed positive anti-HIV antibody test, therefore the statement was removed to accurately reflect the current AbbVie monitoring practice.*

- Update Section 3.19 to indicate that the first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed, with the exception of the PK blood draw.

  Rationale: *To clarify that Baseline PK draw should be performed post-dose.*

- Update Section 3.19 to indicate that subjects should be instructed to administer their dose at the site during the study visit and not at home prior to the visit; however, the subject should follow the regular dosing schedule if study drug administration is normally after the time of the scheduled study visit.

  Rationale: *To clarify that the dose on the study day visit should be administered at the site to allow appropriate collection of PK samples in relation to the dosing time.*

- Update Section 3.20 to add "unless performed at a local laboratory" to indicate when a lab re-test will be considered an Unscheduled Visit.

  Rationale: *To provide further clarification regarding on-study unscheduled visits.*

- Update Section 4.1 to add language regarding toxicity management for abnormal labs and that additional supplemental eCRFs (hepatic and renal) may need to be completed.

  Rationale: *To provide clarification regarding additional supplemental eCRFs required for toxicity management for abnormal labs, as described in Protocol Section 6.2.*

- Update Section 7.1 to clarify the question in the PaGIC-V Example to "Since the start of the treatment you've received in this study, your vitiligo is…".

  Rationale: *To clarify the question since this is a pill and therefore "your vitiligo in areas treated with the study" would not apply.*

- Update Section 7.1 to provide numerical score rate response options of 0 – 4 for the T-PaGVA and F-PaGVA scales.

  Rationale: *To correct the T-PaGVA and F-PaGVA scales as score rate (0 – 4) was missing.*

- Update Section 7.2 to update the Vitiligo History Form Example wording from "any other family member" to "any other biological family member."

  Rationale: *To provide a necessary correction on the paper version of the form.*

- Update Section 7.2 and Section 7.3 to provide more recent versions of the T-VASI, F-VASI, VES, ICVA and Individual Components of Face Examples, and to provide explanation that additional information containing instructions will be provided to the sites.

  Rationale: *To keep this section current.*