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Protocol for Study M16-045 – Measure Up 1

Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Adolescent and Adult Subjects

VERSION:	6.0	DATE:	28 January 2021
SPONSOR:	For Non-EU Countries:* AbbVie Inc. For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie)	PLANNED NUMBER OF SITES:	220
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EUDRACT:	2017-005125-20

FULL TITLE: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis

Incorporating Versions 1.0, 1.01 (VHP Countries), 1.02 (Canada), 2.0, 3.0, 4.0, 5.0, 5.1 (VHP Countries), and 6.0 and Administrative Change 1

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

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

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

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

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1 SYNOPSIS

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis	
Background and Rationale:	Evidence suggests that inhibition of Janus kinase (JAK)-mediated pathways may be a promising approach for the treatment of subjects with moderate to severe atopic dermatitis (AD). Current treatment paradigms for AD suggest that there is a need for additional treatment options for patients. More selective JAK inhibitors may decrease the risk for infection (including viral reactivation) and/or malignancy that are observed with pan JAK inhibitors. AbbVie is developing a small molecule inhibitor of JAK, upadacitinib, that may address the current needs for subjects with AD. The second generation of JAK inhibitors, with different selectivity profiles against JAK1, JAK2, JAK3, and Tyrosine kinase 2 (Tyk2), is in development. Upadacitinib (ABT-494) is a novel selective JAK1 inhibitor being developed for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC), Crohn's disease (CD), and AD. In an in vitro setting, upadacitinib potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit-risk profile in subjects with AD. Results from a Phase 2 study in AD showed that upadacitinib doses of 15 mg to 30 mg per day had efficacy and safety profile that can benefit patients with moderate to severe AD.
Objective(s) and Endpoint(s):	To assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy. The co-primary endpoints to demonstrate superiority of each upadacitinib dose vs. placebo are: • Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16; • Proportion of subjects achieving validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) of 0 or 1 with at least two grades of reduction from Baseline at Week 16.
Investigator(s):	Multi-center; investigator information on file at AbbVie.
Study Site(s):	Approximately 220 sites globally.
Study Population and Number of Subjects to be Enrolled:	Approximately 810 adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy are planned (main study). Subjects who are ≥ 12 and < 18 years of age at the time of the Screening visit will be considered adolescents for the duration of the study. Upon completion of enrollment of 810 subjects in the main study, a supplemental study will continue to enroll adolescent subjects

	(adolescent sub-study) until a total of 180 adolescent subjects are enrolled in the overall study (main study + adolescent sub-study).
Investigational Plan:	A Phase 3, randomized, double-blind, placebo-controlled multicenter study.

Key Eligibility Criteria:	Consent and Demographics
	• Subject must be ≥ 12 years old and ≤ 75 years old at Screening.
	• Body weight ≥ 40 kg at the Baseline Visit for subjects between ≥ 12 and < 18 years of age.
	AD Disease Activity
	• Chronic AD with onset of symptoms at least 3 years prior to Baseline and subject meets Hanifin and Rajka criteria.
	• Subject meets all of the following disease activity criteria:
	  • Eczema Area and Severity Index score ≥ 16 at the Screening and Baseline Visits;
	  • Validated IGA for AD score ≥ 3 at the Screening and Baseline Visits;
	  • ≥ 10% body surface area of AD involvement at the Screening and Baseline Visits;
	  • Baseline weekly average of daily Worst Pruritus Numerical Rating Scale (NRS) ≥ 4. Note: The Baseline weekly average of daily Worst Pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline Visit. A minimum of 4 daily scores out of the 7 days is needed.
	• Subject has applied a topical emollient (moisturizer) twice daily for at least 7 days before the Baseline Visit. Note: Subject may use prescription moisturizers or moisturizers containing ceramide, urea, filaggrin degradation products or hyaluronic acid if such moisturizers were initiated before the Screening Visit.
	• Documented history (within 6 months prior to the Baseline Visit) of inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) OR documented systemic treatment for AD within 6 months prior to the Baseline Visit OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
	Prior/Concomitant Therapy
	• No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, abrocitinib [PF-04965842], and filgotinib).
	• No prior exposure to dupilumab.
	• Subjects must not have used the following AD treatments within the specified timeframe prior to Baseline Visit:

	• Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, interferon-γ, and mycophenolate mofetil within 4 weeks; • Targeted biologic treatments (refer to within 5 half-lives [if known]) or within 12 weeks, whichever is longer; • Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks; • Oral or parenteral traditional Chinese medicine within 4 weeks; • Topical treatments (with the exception of topical emollient treatments), including but not limited to TCS, TCI, or topical PDE4-inhibitors within 7 days.
Study Drug and Duration of Treatment:	Subjects will be randomized in a 1:1:1 ratio to receive daily oral doses of upadacitinib (15 mg or 30 mg) or placebo. At the end of the 16 week double-blind treatment period, subjects in the placebo group will be re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib (15 mg or 30 mg). At the end of the 16 week double-blind treatment period, subjects originally in the 15 mg once daily (QD) or 30 mg QD upadacitinib groups will continue to receive their daily dose of upadacitinib 15 mg or 30 mg for up to Week 260.
Date of Protocol Synopsis:	28 January 2021

2 INTRODUCTION

2.1 Background and Rationale

Why This Study Is Being Conducted

Evidence suggests that inhibition of Janus kinase (JAK)-mediated pathways may be a promising approach for the treatment of subjects with moderate to severe atopic dermatitis (AD). Current treatment paradigms for AD suggest that there is a need for additional treatment options for patients. More selective JAK inhibitors may decrease the risk for infection (including viral reactivation) and/or malignancy that are observed with pan JAK inhibitors or less selective JAK inhibitors. AbbVie is developing a small molecule inhibitor of JAK, upadacitinib, that may address the current needs for subjects with AD.

The second generation of JAK inhibitors, with different selectivity profiles against JAK1, JAK2, JAK3, and tyrosine kinase 2, is in development.[1] Upadacitinib (ABT-494) is a novel selective JAK1 inhibitor being developed for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC), Crohn's disease (CD), and AD. In an in vitro setting, upadacitinib potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit-risk profile in subjects with AD. In the upadacitinib Phase 2 AD study, a statistically significant difference in the mean percent change from Baseline in EASI score at Week 16 (primary endpoint) was observed for 7.5 mg (–39.4%; $P = 0.032$ vs placebo), 15 mg (–61.7%; $P < 0.001$ vs placebo) and 30 mg (–74.4%; $P < 0.001$ vs placebo) groups compared with placebo (–23.0%). Through Week 16 (Period 1), the percentages of subjects with AEs, SAEs, severe AEs, and AEs leading to discontinuation were similar across treatment groups. There were no deaths reported during Period 1. Additionally, upadacitinib was studied in rheumatoid arthritis with the results of two Phase 2 studies and two Phase 3 studies available as peer-reviewed manuscripts.[2,3,4,5] Results from a Phase 2 study in AD showed that upadacitinib doses of 15 mg to 30 mg per day had efficacy and safety profile that can benefit patients with moderate to severe AD.

Clinical Hypothesis

Upadacitinib is expected to provide better efficacy compared to placebo and be well tolerated in adolescent and adult subjects with moderate to severe AD.

2.2 Benefits and Risks to Subjects

Treatment of AD in adolescent and adult subjects depends on the extent and severity of disease. Topical agents alone are commonly used for mild to moderate cases. The most commonly used topical agents are corticosteroids, calcineurin inhibitor agents, and moisturizers. When topical therapies are insufficient for treating the signs and symptoms of AD, systemic therapy or phototherapy are generally added to topical agents.[6]

Treatment guidelines developed by the American Academy of Dermatology recommend the use of systemic immunomodulatory agents for subjects in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease. These guidelines recognize

that insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication.[7] Importantly, in addition to the lack of well-controlled efficacy data supporting their use in moderate to severe AD, the duration of use of many traditional systemic immunomodulatory agents are limited due to cumulative toxicity.

More recently, dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling, has been approved for the treatment of moderate to severe eczema (AD) in adults. Although dupilumab addresses the needs of some patients with moderate to severe AD, a large unmet need still exists in this population since, in the dupilumab Phase 3 studies (even when combined with TCS), fewer than 40% of patients achieved 0 or 1 on the Investigator's Global Assessment (IGA) scale; therefore, 60% or more of patients continued to experience significant symptoms on dupilumab therapy.[8,9] Nearly 50% of dupilumab subjects who were IGA 0 or 1 responders at Week 16 became non-responders by Week 52.[10]

At this time very few systemic agents are approved for AD and, of those, cyclosporin A and oral prednisone are not suitable for long-term use. Thus, there is a high unmet need for a significant number of patients with an inadequate response to topical agents.

Upadacitinib is a novel selective orally available JAK1 inhibitor with the potential to decrease Th2 mediated skin inflammation and itch while having minimal inhibitory effects on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.[11,12] Events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib.

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.

Primary results from the ongoing Phase 2 study demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected doses for Phase 3 (15 mg and 30 mg once daily [QD]) compared to placebo in subjects with moderate to severe AD. Taken together, the efficacy and safety data from the Phase 2 AD study and cumulative safety data from ongoing Phase 2 and 3 programs in other disease indications support further development of upadacitinib in subjects with moderate to severe AD.

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.

For further details, please see findings from completed studies, including safety data in upadacitinib Investigator's Brochure.[13]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

To assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy.

3.2 Co-Primary Endpoints

The co-primary endpoints to demonstrate superiority of each upadacitinib dose vs. placebo are:

- Proportion of subjects achieving at least a 75% reduction in Eczema Area and Severity Index (EASI 75) from Baseline at Week 16;
- Proportion of subjects achieving validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) of 0 or 1 with at least two grades of reduction from Baseline at Week 16.

3.3 Secondary Endpoints

The following key secondary endpoints will be analyzed to demonstrate superiority of each upadacitinib dose vs. placebo, unless otherwise specified.

Key Secondary Endpoints for EU/EMA regulatory purposes are:

- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus Numerical Rating Scale (NRS) ≥ 4 from Baseline at Week 16 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving EASI 90 at Week 16;
- Percent change from Baseline of Worst Pruritus NRS at Week 16;
- Percent change in EASI from Baseline at Week 16;
- Proportion of subjects achieving EASI 75 at Week 2;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 1 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in Patient Oriented Eczema Measure (POEM) ≥ 4 from Baseline at Week 16 for subjects with POEM ≥ 4 at Baseline;
- Proportion of subjects age ≥ 16 years old at screening achieving an improvement (reduction) in Dermatology Life Quality Index (DLQI) ≥ 4 from Baseline at Week 16 for subjects with DLQI ≥ 4 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 30 mg vs. placebo);

- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 3 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 15 mg vs. placebo);
- Proportion of subjects experiencing a flare, characterized as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, during double-blind treatment period (DB Period);
- Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16;
- Proportion of subjects achieving a Hospital Anxiety and Depression Scale-anxiety (HADS-A) < 8 and Hospital Anxiety and Depression Scale-depression (HADS-D) < 8 at Week 16 among subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥ 12 (minimal clinically important difference [MCID]) from Baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) skin pain score ≥ 4 (MCID) from Baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS 7-item total symptom score (TSS-7) ≥ 28 (MCID) from Baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline; ADerm-SS TSS-7 is defined as the algebraic sum of the responses to items 1 – 7 of the ADerm-SS;
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 (MCID) from Baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline;
- Proportion of subjects achieving EASI 100 at Week 16;
- Proportion of subjects age ≥ 16 years old at screening achieving DLQI score of 0 or 1 at Week 16 for subjects with DLQI > 1 at Baseline;

Key secondary endpoints for US/FDA regulatory purposes are:

- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 16 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving EASI 90 at Week 16;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;
- Proportion of subjects achieving EASI 75 at Week 2;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Week 1 for subjects with Worst Pruritus NRS ≥ 4 at Baseline;

- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 2 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 30 mg vs. placebo);
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline at Day 3 for subjects with Worst Pruritus NRS ≥ 4 at Baseline (upadacitinib 15 mg vs. placebo);
- Proportion of subjects experiencing a flare, characterized as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, during DB Period;
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS sleep domain score ≥ 12 (MCID) from Baseline at Week 16 for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥ 4 (MCID) from Baseline at Week 16 for subjects with ADerm-SS skin pain score ≥ 4 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS TSS-7 ≥ 28 (MCID) from Baseline at Week 16 for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline at Week 16 for subjects with ADerm-IS emotional state domain score ≥ 11 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS daily activities domain score ≥ 14 (MCID) from Baseline at Week 16 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline;
- Proportion of subjects achieving EASI 100 at Week 16;

3.4 Additional Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all visits other than those listed above. In addition, the following endpoints to demonstrate superiority of each upadacitinib dose vs. placebo will be evaluated at all visits:

- Change from Baseline in EASI;
- Change from Baseline in Worst Pruritus NRS;
- Proportion of subjects achieving EASI 50 at Week 1;
- Proportion of subjects achieving Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline;
- Proportion of subjects achieving at least a 50%/75%/90% reduction in SCORAD (SCORAD 50/75/90) from Baseline;
- Proportion of subjects experiencing flare, characterized as a clinically meaningful worsening in EASI, defined as an increase of EASI by ≥ 6.6 from Baseline for subjects with EASI ≤ 65.4 at Baseline, by visit after Week 16;

- Among responders at Week 16, proportion of subjects experiencing loss of response after Week 16 until Week 52, by visit and overall; loss of response is defined as a loss of at least 50% of the EASI response at Week 16 and a vIGA-AD score of 2 or higher; for this analysis only, responders will be defined as subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from Baseline and EASI 75 at Week 16;
- Change from Baseline in body surface area (BSA);
- Change and percent change from Baseline in HADS-A;
- Change and percent change from Baseline in HADS-D;
- Change and percent change from Baseline in HADS total score;
- Percent Change from Baseline in Hand eczema severity index (HECSI);
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS 11-item total symptom score (TSS-11) ≥ 44 (MCID) from Baseline for subjects with ADerm-SS TSS-11 ≥ 44 at Baseline; ADerm-SS TSS-11 is defined as the algebraic sum of the responses of items 1 – 11 of the ADerm-SS;
- Change and percent change from Baseline in ADerm-SS TSS-7, ADerm-SS TSS-11, and skin pain score;
- Proportion of subjects achieving ADerm-SS skin pain score of 0 for subjects with ADerm-SS skin pain score > 0 at Baseline;
- Change and percent change from Baseline in ADerm-IS sleep domain score, emotional state domain score, and daily activities domain score;
- Change and percent change from Baseline in POEM;
- Proportion of subjects achieving POEM sleep item score of 0 for subjects with POEM sleep item score > 0 at Baseline;
- Change and percent change from Baseline in DLQI among subjects age ≥ 16 years old at screening;
- Proportion of subjects age < 16 years old at screening achieving Children's Dermatology Life Quality Index (CDLQI) score of 0 or 1 for subjects with CDLQI score > 1 at Baseline;
- Change and percent change from Baseline in CDLQI among subjects age < 16 years old at screening;
- Change and percent change from Baseline in Work Productivity and Activity Impairment Index: Atopic Dermatitis (WPAI:AD) domain scores (absenteeism, presenteeism, activity impairment, overall work productivity);
- Change and percent change from Baseline in EuroQoL Dimensions 5 Levels (EQ-5D-5L);
- Change and percent change from Baseline in Short Form-36 Health Survey (SF-36) summary scores (physical component summary, mental component summary) and scale scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, social role functioning, mental health);
- Change and percent change from Baseline in Patient Global Impression of Severity (PGIS);

- Proportion of subjects who report symptoms to be "Minimal" or "Absent" on the PGIS for subjects who did not report symptoms to be "Minimal" or "Absent" at Baseline;
- Proportion of subjects who are "Very much improved" or "Much improved" on the Patient Global Impression of Change (PGIC);
- Proportion of subjects who are "Extremely satisfied" or "Very satisfied" on the Patient Global Impression of Treatment (PGIT) for subjects who are not "Extremely satisfied" or "Very satisfied" on the PGIT at Baseline.
- Proportion of subjects achieving EASI 50;
- Proportion of subjects achieving a vIGA-AD of 0 with a reduction from Baseline of ≥ 2 points;

3.5 Safety Endpoints

Safety evaluations for the duration of the study include: treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) of special interest (AESIs), AEs leading to discontinuation, vital signs, and laboratory tests.

3.6 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples will be collected from subjects at select sites at the visits indicated in Appendix D. Using the data available from these subjects, a nonlinear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of upadacitinib oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. Data from this study may be combined with data from other studies for the population PK analyses.

3.7 Biomarker Samples

The analyses of optional biomarker samples may include but are not limited to genetic markers that will help to understand the subject's disease and response to upadacitinib. Genes of interest may include those associated pharmacokinetics (drug metabolizing enzymes, drug transport proteins), genes within the target pathway (JAK, Tyrosine kinase 2 [Tyk2], TNF), or other genes believed to be related AD, and other inflammatory diseases (FLG, CLDN1, HLA). Research may also include epigenetic changes in DNA that may associate with the subject's response to treatment or disease. Samples for RNA and proteomics will be used to research if any genetic variants result in changes to gene expression or protein concentrations. For any samples collected in Germany, the research will be restricted to upadacitinib and AD.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3, randomized, double-blind, placebo-controlled multi-center study that will evaluate upadacitinib in adolescents (12 – 17 years of age) and adults (18 – 75 years of age) with moderate to severe AD who are candidates for systemic therapy. Eligible subjects must have a documented history of inadequate response to treatment with topical AD treatments or documented use of systemic treatment for AD or for whom topical treatments are otherwise medically inadvisable.

The study is comprised of a 35-day Screening Period, a 16-week DB Period, a Blinded Extension period of up to Week 260, and a 30-day Follow-up Visit.

Subjects who meet eligibility criteria in the main study will be randomized in a 1:1:1 ratio to receive daily oral doses of upadacitinib 15 mg (N = 270) or of upadacitinib 30 mg (N = 270) or matching placebo (N = 270). Upon completion of enrollment of 810 subjects in the main study, a supplemental study will continue to enroll adolescent subjects (adolescent sub-study) until a total of 180 adolescent subjects are enrolled in the overall study (main study + adolescent sub-study). Randomization for the main study will be stratified by baseline disease severity (moderate [vIGA-AD 3] vs. severe [vIGA-AD 4]), by geographic region (US/Puerto Rico/Canada, Japan, China, and Other), and by age (adolescent [ages 12 to 17] versus adult [ages 18 to 75]). The separate randomization for the adolescent sub-study will be stratified by baseline disease severity (moderate [vIGA-AD 3] vs. severe [vIGA-AD 4]) and by geographic region (US/Puerto Rico/Canada and Other).

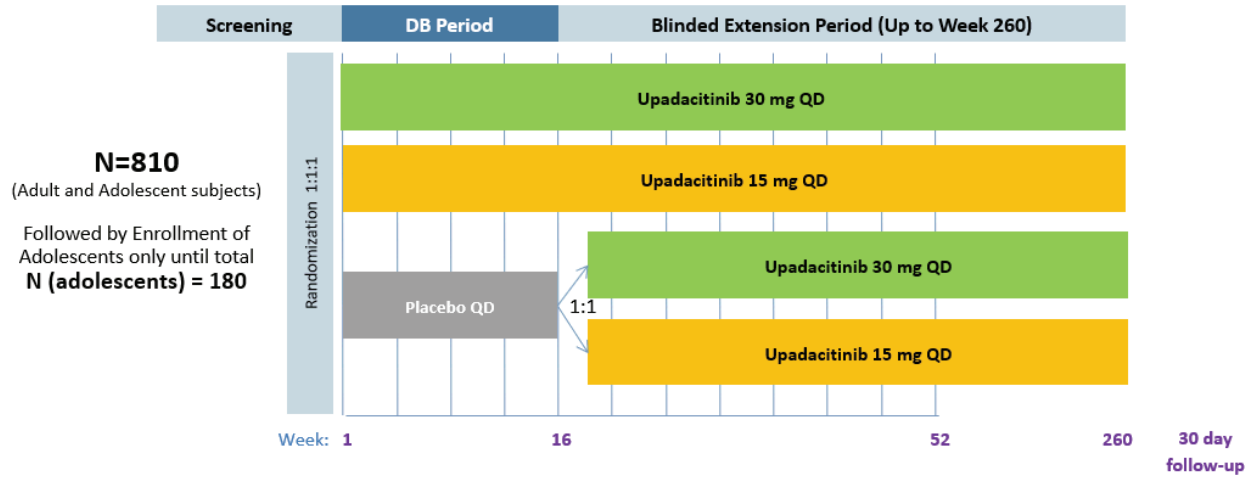
At Week 16, subjects in the placebo group will be re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg during the Blinded Extension period. Subjects originally in the 15 mg QD and 30 mg QD upadacitinib group will continue their treatment into the Blinded Extension period up to the Week 260 visit. Starting at the Week 4 visit, rescue treatment for AD may be provided at the discretion of the investigator if medically necessary (further details are available in Section 5.4).

Information on the Data Monitoring Committee (DMC) and Cardiovascular Adjudication Committee (CAC) are described in Section 6.3.

The Primary Analysis for the main study will be conducted after all ongoing subjects have completed Week 16. After the Primary Analysis, an additional analysis for the main study will be conducted when the required safety exposure target is reached. In addition, a Week 52 analysis of the main study will be performed after all ongoing subjects complete the Week 52 visit. Furthermore, a Primary Analysis for the adolescent population (including the adolescent subjects from the main study and the adolescent sub-study) will be conducted after all ongoing adolescent subjects have completed Week 16. An additional analysis for the adolescent population will be conducted after all ongoing adolescent subjects have provided at least 1 year of upadacitinib exposure. In addition, interim database locks may be performed after all subjects (main study and adolescent sub-study) have completed the study activities up to the relevant timepoints after Week 140. The study sites and subjects will remain blinded to treatment assignments for the duration of the study.

The schematic of the overall study is shown in Figure 1.

Figure 1. Study Schematic



DB = double-blind; QD = once daily

Note: This schematic applies to both the main study and adolescent sub-study.

4.2 Discussion of Study Design

Choice of Control Group

Placebo has been selected as the appropriate control group since, as discussed in Section 2.2, there is no established standard for systemic therapy in moderate to severe AD. There is no anticipated medical risk for subjects randomized to placebo and if needed, rescue treatment will be available for these subjects.

Appropriateness of Measurements

Standard clinical and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with AD. Other than the biomarker analyses which are exploratory, all 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, especially in adolescent subjects. 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 2 unsuccessful attempts for venipuncture, consider requesting the subject to return at a later time for the blood sample collection within the timeframe allowed by the protocol.

Suitability of Subject Population

The target study population for this study represents an adolescent and adult AD population with moderate to severe disease activity appropriate for systemic therapies.

Subjects who are between ≥ 12 and < 18 years of age at the time of the Screening visit will be considered adolescents for the duration of the study.

Inclusion of Adolescent Subjects 12 to 17 Years of Age

The adult phase of AD begins at puberty and frequently continues into adulthood.[14] In adolescents and adults, the disease presents similarly, typically involving the flexural folds, face, neck, upper arms and back, and dorsal surface of the hands and feet with few notable pathogenetic differences between these age groups.[15,16] While there are no published studies comparing AD disease factors and treatment between adolescents 12 to 17 years of age and adults ≥ 18 years of age, published guidelines in both the United States and Europe make no distinctions in the diagnosis, assessment, and treatment of AD in adolescents and adults.[6,7,16]

The rationale for selection of doses for adolescents is detailed below. To confirm dose assumptions, PK evaluation will be performed for adolescents and adults in the study.

Selection of Doses in the Study

This study will evaluate two doses of Upadacitinib (15 mg and 30 mg QD). The selection of these doses was informed by the analyses of the 16-week safety, efficacy, and exposure-response data from Period 1 of the Phase 2 AD Study M16-048, which evaluated 3 doses of upadacitinib (7.5 mg, 15 mg or 30 mg QD) versus placebo. In addition, available PK, pharmacodynamic, and safety data from upadacitinib studies in other disease indications were used to support the selection of these doses.

The Phase 2 study results demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected doses (15 mg and 30 mg QD) compared to placebo in subjects with moderate to severe AD. A statistically significant difference in the mean percent change from Baseline in EASI score at Week 16 (primary endpoint) was observed for 7.5 mg (–39.4%; $P = 0.032$ vs placebo), 15 mg (–61.7%; $P < 0.001$ vs placebo) and 30 mg (–74.4%; $P < 0.001$ vs placebo) groups compared with placebo (–23.0%). Through Week 16 (Period 1), the percentages of subjects with AEs, SAEs, severe AEs, and AEs leading to discontinuation were similar across treatment groups. There were no deaths reported during Period 1. Preliminary exposure-response analyses for Period 1 of the Phase 2 study show that the percentage of subjects achieving EASI 75, EASI 90, or IGA 0/1 increased with increasing upadacitinib plasma exposures. Simulations using preliminary exposure-response models indicate that doses lower than 15 mg QD (e.g., 7.5 mg QD) are not predicted to provide adequate efficacy in subjects with moderate-to-severe AD.

Bodyweight was not found to be correlated with upadacitinib apparent clearance within the evaluated range of 39 kg to 152 kg in the preliminary population-pharmacokinetic analysis across healthy volunteers and in subjects with RA, CD, and AD. Consistent with this finding, upadacitinib estimated apparent clearance was found to be similar between adult subjects with low body weight (< 50 kg) and rest of the subjects across Phase 1 and 2 studies (bodyweight greater than or equal to 50 kg). Adult subjects with CD have been evaluated with chronic dosing of upadacitinib up to 24 mg twice a day using the immediate release formulation (exposures equivalent to that of 60 mg QD regimen using the extended release tablet formulation) with acceptable safety profile. Therefore, there is no anticipated risk resulting from higher exposures for adult subjects weighing less than 40 kg receiving the 30 mg QD dose in the AD clinical trials. As for adolescents, given that no adolescents have been exposed to

upadacitinib before, the 40 kg cutoff is implemented as an additional safety precaution for this population only.

Among the cytochrome P450s (CYPs), upadacitinib is mainly eliminated via CYP3A mediated metabolism (approximately 24% and 38% of upadacitinib immediate-release dose is excreted as unchanged upadacitinib in urine and feces, respectively and 34% is excreted as metabolites). Literature suggests that maturation of the CYP3A activity in children 2 years and above is similar to that of adults.[17] Therefore, upadacitinib clearance is not expected to be different between adolescents and adults because of age.

Given the evidence in literature with regards to comparable maturation of the CYP3A activity in adolescents relative to adults and that upadacitinib clearance (the key pharmacokinetic parameter that drives the steady state exposures [area under the plasma drug concentration-time curve]) was shown not to be correlated with the bodyweight (within the range of 39 kg to 152 kg), it is estimated that upadacitinib exposures will be comparable within this body weight range in adolescents and adult subjects with atopic dermatitis.

In summary, exposures associated with upadacitinib 15 mg QD and 30 mg QD using the once-daily formulation are predicted to be effective and have an acceptable safety profile across the proposed age range for the treatment of subjects with moderate to severe AD.

Placebo Duration Rationale

The 16-week DB Period is deemed to be a sufficient duration to be able to test the superiority of upadacitinib versus placebo for achieving the co primary endpoints (EASI 75 and vIGA-AD) at Week 16 and several secondary endpoints, while minimizing undue burden for subjects. The placebo-controlled period will allow for a 16-week assessment of efficacy and safety versus a control group. To ensure appropriate medical care for subjects, starting from Week 4, all subjects with an inadequate response may be rescued with escalating therapies ranging from higher potency topical agents to systemic agents of the investigator's choice (see Rescue Therapy in Section 5.4 for further details).

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 and Demographics

- 1. Subject must be ≥ 12 years old and ≤ 75 years old at Screening Visit. Adolescent subjects below the age of 18 years old will be enrolled if approved by the country or regulatory/health authority. If these approvals have not been granted, only subjects ≥ 18 years old at the Screening Visit will be enrolled.

- 2. Adult subjects ≥ 18 years of age at Screening Visit must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and comply with the requirements of this study protocol.

  In Japan, if a subject is under 20 years of age, then the subject and their parent or legal guardian must voluntarily sign and date an informed consent.
- 3. For subjects ≥ 12 years old and < 18 years old at Screening Visit: Parent or legal guardian, as required, has voluntarily signed and dated an informed consent form, approved by an IEC, after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. Subjects will be included in all discussions in order to obtain verbal/and or written assent. Parent/legal guardian and subject must comply with the requirements of this study protocol. If a subject becomes of legal age during the course of the study, that subjects will need to be consented using the approved informed consent form.
- 4. Body weight ≥ 40 kg at the Baseline Visit for subjects between ≥ 12 and < 18 years of age.
- 5. Subject is judged to be in general good health (other than AD) 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.

AD Disease Activity

- 6. Chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria.[18]
- 7. Subject meets all of the following disease activity criteria:
  - EASI score ≥ 16 at the Screening and Baseline Visits;
  - vIGA-AD score ≥ 3 at the Screening and Baseline Visits;
  - ≥ 10% BSA of AD involvement at the Screening and Baseline Visits;
  - Baseline weekly average of daily Worst Pruritus NRS ≥ 4. Note: The baseline weekly average of daily Worst Pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline Visit. A minimum of 4 daily scores out of the 7 days is needed.
- 8. Subject has applied a topical emollient (moisturizer) twice daily for at least 7 days before the Baseline Visit. Note: Subject may use prescription moisturizers or moisturizers containing ceramide, urea, filaggrin degradation products or hyaluronic acid if such moisturizers were initiated before the screening visit.
- 9. Documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or TCI OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).

Contraception

- 10. Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at the Baseline Visit prior to study drug dosing. Note: subjects with borderline pregnancy test at Screening must have a serum pregnancy test ≥ 3 days later to determine eligibility (refer to Section 5.10 for details).
- 11. If female, subject must be postmenopausal OR permanently surgically sterile OR for females of childbearing potential practicing at least one protocol specified method of birth control (refer to Section 5.2), that is effective from the Baseline Visit through at least 30 days after the last dose of study drug.
- 12. Female subject must not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 30 days after the last dose of the study drug.
- 13. Additional local requirements may apply.

Prior/Concomitant Therapy

- 14. No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, abrocitinib [PF-04965842], and filgotinib).
- 15. No prior exposure to dupilumab.
- 16. Subjects must not have used the following AD treatments within the specified timeframe prior to Baseline Visit:
  - Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-γ and mycophenolate mofetil within 4 weeks;
  - Targeted biologic treatments (refer to within 5 half-lives [if known]) or within 12 weeks, whichever is longer;
  - Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks;
  - Oral or parenteral traditional Chinese medicine within 4 weeks;
  - Marijuana use within 2 weeks;
  - Topical treatments (with the exception of topical emollient treatments, described in Eligibility Criterion 8), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days.
- 17. Subjects must not have received any live vaccine within 4 weeks (or longer if required locally) prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks (or longer if required locally) after the last dose of study drug.

  In Japan, subject must not have received any live vaccine within 8 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 8 weeks after the last dose of study drug.

- 18. No systemic use of known strong CYP3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to Table 1 in Section 5.3 for examples of commonly used strong CYP3A inhibitors and inducers).
- 19. No treatment with any investigational drug of chemical or biologic nature within 4 weeks or five half-lives of the drug (whichever is longer) prior to Baseline Visit or is currently enrolled in another clinical study.

  In China, subject must have no current or past history of infection including active syphilis infection or confirmed syphilis antibody positive (+).

Medical History

- 20. Subjects must not have 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 (GFR) of < 40 mL/min/1.73 m^2 by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula for adult subjects or by Schwartz equation for adolescent subjects;
  - Total white blood cell count (WBC) < 2,500/µL;
  - Absolute neutrophil count (ANC) < 1,500/µL;
  - Platelet count < 100,000/µL;
  - Absolute lymphocyte count < 800/µL;
  - Hemoglobin < 10 g/dL.
- 21. No current or past history of the following:
  - Other active skin diseases or skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline Visit or would interfere with the appropriate assessment of AD lesions;
  - History of recurrent herpes zoster, or one or more episodes of disseminated herpes zoster;
  - History of one or more episodes of disseminated herpes simplex (including eczema herpeticum);
  - History of known invasive infection (e.g., listeriosis and histoplasmosis);
  - Active human immunodeficiency virus (HIV) or immunodeficiency syndrome. Active HIV is defined as confirmed positive anti-HIV antibody test;
  - Subject has active Tuberculosis (TB) or meets TB exclusionary parameters (refer to Section 5.10 for specific requirements for TB testing);
  - Non-skin related active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral 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;
- Active hepatitis B virus (HBV) or hepatitis C virus (HCV):
  - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects (and for hepatitis B surface antibody positive [+] where mandated per local requirements);
  - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
- In Japan, positive result of beta D glucan or 2 consecutive indeterminate results of beta-D-glucan (screening for pneumocystis jiroveci infection at central lab).

22. Subject must not have any of the following medical conditions:

- Any of the following cardiovascular conditions:
  - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
  - Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
  - Any other unstable clinical condition which, in the opinion of the investigator, would put the subject at risk by participating in the protocol.
- Subject has been a previous recipient of an organ transplant which requires continued immunosuppression;
- History of gastrointestinal (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;
- History of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix;
- History of clinically significant medical conditions or any other reason, which in the opinion of the investigator, would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.

Miscellaneous

23. No history of an allergic reaction or significant sensitivity to constituents of the study drugs (or its excipients) and/or other products in the same class.

24. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.

5.2 Contraception Recommendations

Contraception Requirements for Females

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

Surgically sterile is defined as:

- bilateral oophorectomy (surgical removal of both ovaries); or
- bilateral salpingectomy (surgical removal of both fallopian tubes); or
- hysterectomy (surgical removal of uterus)

Postmenopausal is defined as:

- Age > 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.

If the female subject is ≤ 55 years of age, postmenarchal, and has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.

- If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol-specified contraception is required.
- If the FSH is tested and the result is consistent with postmenopausal status, contraception is not required.
- If the FSH is tested and the result is consistent with premenopausal status, contraception is required, and pregnancy testing requirements for women of childbearing potential must be followed (see below).

A female who does not meet the definition of postmenopausal or permanently surgically sterile, and who is postmenarchal or pubertal and has not yet had menses (premenarchal, Tanner stage 3 or higher), is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control that is effective from Baseline Visit (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Bilateral tubal occlusion/ligation.

- Vasectomized partner(s) provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device.
- Intrauterine hormone-releasing system (IUS).
- True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., using calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable.

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

For female adolescents not considered as having childbearing potential at baseline, if during the course of the study a female adolescent becomes of childbearing potential, she is required to take the recommended contraception measures (including true abstinence if acceptable per local requirements) listed above.

If during the course of the study a female becomes surgically sterile or postmenopausal (defined above) and complete documentation is available, contraceptive measures as defined above are no longer required. It is important to note that contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapy upadacitinib.

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

Additional local requirements may apply. In Japan, a Japanese female who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control that is effective from Baseline Visit (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Bilateral tubal ligation
- Vasectomized partner(s) provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the females of childbearing potential trial participant.
- Intrauterine device.
- Intrauterine hormone-releasing system.

- True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., using calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable.

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

5.3 Prohibited Medications and Therapy

Medications to treat chronic or acute conditions are permitted (with the exception of the treatments listed below). Prohibited medications and therapy are allowed after permanent discontinuation of study drug or after completion of study drug treatment.

JAK Inhibitors

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

Targeted Biologic Therapies

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:

- abatacept
- adalimumab
- anakinra
- belimumab
- certolizumab pegol
- dupilumab
- efalizumab
- etanercept
- golimumab
- guselkumab
- infliximab
- ixekizumab
- natalizumab
- omalizumab
- rituximab
- secukinumab

- tocilizumab
- ustekinumab

See also Rescue Therapy in Section 5.4 for further details on systemic rescue.

Other Non-Biologic Systemic Therapy

Non-corticosteroid systemic therapies for the treatment of AD are prohibited concomitant with study drug, including but not limited to:

- methotrexate
- cyclosporine
- azathioprine
- PDE4-Inhibitors (e.g., apremilast)
- mycophenolate mofetil

See also Rescue Therapy in Section 5.4 for further details on systemic rescue.

Corticosteroids

Inhaled, ophthalmic drops and nasal corticosteroid formulations are allowed throughout the study. Subjects may be treated with systemic corticosteroids for non-AD reasons if medically necessary after Week 16. Any subject who receives systemic corticosteroid for more than 2 consecutive weeks regardless of the dosage of corticosteroid should permanently discontinue study drug. Subjects who permanently discontinue study drug are encouraged to continue to participate in the study (no study drug given) and will complete the schedule of study visits and assessments.

Intravenous, intramuscular, intralesional corticosteroids are prohibited throughout the study for treatment of AD. The use of oral corticosteroids for routine treatment for AD during the study is prohibited. See Rescue Therapy in Section 5.4 for further details on corticosteroid rescue allowances.

Investigational Drugs

Subjects who have been treated with any investigational drug within 4 weeks or five 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.

Phototherapy, Tanning Booth, and Extended Sun Exposure

Ultra-violet (UV) B or UVA phototherapy including PUVA or laser therapy for at least 4 weeks prior to the Baseline visit and during the study are not allowed. Also not allowed is tanning booth use or extended sun exposure that could affect disease severity or interfere with disease assessments for at least 4 weeks prior to the Baseline visit and during the study.

Topical Therapy

No topical treatments for AD should be started through Week 16 except for rescue treatment (see Rescue Therapy in Section 5.4). This includes but is not limited to calcineurin inhibitors, corticosteroids, prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin. Topical emollient treatments are allowed per Eligibility Criterion 8.

Starting at the Week 16 Visit, the use of any concomitant topical medication for atopic dermatitis can be administered per investigator discretion.

Topical anti-infectives, topical antihistamines, and bleach baths are not prohibited during the study if they are used for reasons other than AD. Topical anti-infectives, topical antihistamines, and bleach baths may be used in the first 16 weeks of the study for AD if they were used in the 6 months prior to the Screening visit.

If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the AbbVie Therapeutic Area Scientific Director (TA SD).

Vaccines

If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) at least 4 weeks (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. Live vaccines are not permitted during study participation before week 52 and including up to 4 weeks (or longer if required locally) after the last dose of study drug for those who discontinued study drug at or before Week 52. Examples of live vaccines include, but are not limited to, the following:

- Bacille Calmette-Guérin
- herpes zoster (Zostavax)
- measles-mumps-rubella or measles-mumps-rubella-varicella
- monovalent live attenuated influenza A (H1N1) (intranasal)
- oral polio vaccine
- rotavirus
- seasonal trivalent live attenuated influenza (intranasal)
- smallpox
- typhoid
- varicella (chicken pox)
- yellow fever

After week 52, if a live vaccine must be administered during study participation, study drug must be held for at least 30 days prior to the vaccination and at least 30 days after the vaccination (or longer if required locally).

Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines.

In Japan, live vaccines are not permitted during study participation and including up to 8 weeks after the last dose of study drug. If the subject and investigator choose to administer live vaccines, these vaccinations must be completed at least 8 weeks, whichever is longer, before first dose of study drug with appropriate precautions.

Cannabis

Use of medicinal and recreational marijuana is prohibited during the study and subjects must have discontinued use at least 2 weeks prior to Baseline until study drug discontinuation.

Traditional Chinese Medicine

Traditional oral or parenteral Chinese medicine is not permitted during the study as these may interfere with upadacitinib metabolism and exposure and may impact efficacy and safety of upadacitinib treatment. Subjects must have discontinued oral or parenteral traditional Chinese medicine at least 4 weeks prior to the first dose of study drug.

Strong CYP3A Inhibitors or Inducers

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

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. If the subject undergoes elective surgery, see Section 5.8 for allowed study drug interruption parameters.

If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. See Section 5.8 for allowed study drug interruption parameters.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements including folic acid) that the subject is receiving within 28 days prior to screening, or receives during the study, must be recorded.

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before the first dose of study drug with appropriate

precautions and time interval. It is recommended that subjects be up to date for recommended vaccines that are inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and tetanus-diphtheria-acellular pertussis (Tdap). It is recommended that the live herpes zoster vaccine be considered for administration at least 4 weeks before the first dose of study drug in subjects greater than 50 years of age (per label). If the herpes zoster vaccine is to be administered, pre-existing immunity should be confirmed through antibody testing at or prior to screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative the herpes zoster vaccine should not be administered. See Section 5.3 for a list of commonly used live vaccines.

If there are any questions regarding concomitant or prior therapies the AbbVie Therapeutic Area Scientific Director should be contacted who will then discuss with the AbbVie Medical Director and provide a recommendation.

In Japan, it is recommended that the live herpes zoster vaccine be considered for administration at least 8 weeks before the first dose of study drug in subjects greater than 50 years of age (per label).

Prior Therapy

Any systemic treatments for AD since initial diagnosis (as determined through medical history records or through subject or parent or legal representative interview) and any prescribed treatments for AD prior to study entry will be recorded on the electronic case report form (eCRF).

Required Concomitant Medications

Beginning at the screening visit, twice daily use of an additive-free, bland emollient is required for at least 7 days prior to Baseline and during the study until Week 16. Starting at the Week 16 Visit or after premature discontinuation of study drug, the use of emollients can be administered per investigator discretion.

Note: Until Week 16, the subject may use prescription moisturizers or moisturizers containing ceramide, urea, filaggrin degradation products or hyaluronic acid if such moisturizers were initiated before the screening visit.

Rescue Therapy

Starting at the Week 4 visit, rescue treatment for AD may be provided, if medically necessary and the following parameters are met:

- At Week 4 through Week 24: subjects with < 50% reduction in EASI (EASI 50) response at any two consecutive scheduled visits (e.g., at Week 2 and Week 4 with rescue at Week 4; or at Week 20 and Week 24 with rescue at Week 24), compared to the Baseline EASI score.
- After Week 24: subjects with < EASI 50 response at any scheduled or unscheduled visit, compared to the Baseline EASI score.

Investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for those subjects who do not respond adequately after at least 7 days of topical treatment.

Starting at the Week 16 Visit, the use of any concomitant topical medication for atopic dermatitis can be administered per investigator discretion and will no longer be considered as rescue therapy. Only systemic treatments for AD will be considered as rescue therapy for the purposes of statistical analyses of efficacy.

Subjects who receive topical rescue treatment or oral corticosteroids during the study treatment period can continue study drug. Oral corticosteroids are not allowed for routine treatment of AD (see Prohibited Medications and Therapy in Section 5.3). If oral corticosteroids must be used, rescue treatment will be limited to prednisone or prednisolone for up to 1 mg/kg for no more than 2 consecutive weeks. Any subject who receives oral corticosteroid for more than 2 consecutive weeks regardless of the dosage of corticosteroid should permanently discontinue study drug.

If a subject needs rescue treatment with a non-corticosteroid systemic agent (including but not limited to cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, dupilumab) or with an injectable or parenteral corticosteroid, study drug should be permanently discontinued prior to the initiation of rescue systemic agent.

If rescue treatment is medically necessary outside of the parameters described above (i.e., to control intolerable AD symptoms), study drug should be permanently discontinued.

Subjects who permanently discontinue study drug are encouraged to continue to participate in the study (no study drug given) and complete the schedule of study visits and assessments.

Investigators should conduct efficacy and safety assessments (e.g., disease severity scores, safety labs) before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.

5.5 Withdrawal of Subjects and Discontinuation of Study

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time. Subjects who discontinue the study prematurely after randomization will not be replaced. Subjects may discontinue study drug treatment but may choose to continue to participate in the study.

Subjects can request to be discontinued from participating in the study at any time for any reason including, but not limited to, disease progression or lack of response to treatment. The investigator may discontinue any subject's participation at any time for any reason, including but not limited, to disease progression, lack of response to treatment, an AE, safety concerns, or failure to comply with the protocol. Refer to Section 6.2 for additional discontinuation criteria relating to Toxicity Management of serious infections, GI perforation, cardiovascular and thromboembolic events, malignancy, ECG abnormality and select laboratory abnormalities.

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

- Rescue treatment is administered outside of the parameters described in Section 5.4 (Rescue Therapy).
- Oral corticosteroid for more than 2 consecutive weeks.
- Initiation of injectable or parenteral non-corticosteroid systemic rescue therapy for AD.

- Permanent discontinuation from study drug will be mandatory after Week 4 for any subject with an EASI score worsening of 25% or more compared with their Baseline EASI score at any 2 consecutive scheduled study visits after Week 4 (after a trial of rescue treatment, if appropriate; see Rescue Therapy in Section 5.4). For example, permanent study drug discontinuation would apply at Week 8 if EASI score worsening criteria are met at Week 4 and Week 8 without rescue therapy given at Week 4. Permanent study drug discontinuation would apply at Week 12 if EASI score worsening criteria are met at Week 8 and Week 12 with rescue therapy given at Week 4. This rule applies similarly to later timepoints.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator and the AbbVie Therapeutic Area Medical/Scientific Director. *Note: Intentional/prospective deviations from the protocol are not allowed. See Section 5.9 Protocol Deviations.*
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Therapeutic Area Medical/Scientific Director. *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, as determined by the AbbVie Therapeutic Area Medical/Scientific Director. *Note: Intentional/prospective deviations from the protocol are not allowed. See Section 5.9 Protocol Deviations.*
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant or plans to become pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial in consultation with the AbbVie Therapeutic Area Medical/Scientific Director. *Note: Intentional/prospective deviations from the protocol are not allowed. See Section 5.9 Protocol Deviations.*
- 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.
- An ECG change considered clinically significant and with reasonable possibility of relationship to study drug, OR a confirmed absolute Fridericia's correction formula (QTcF) value > 500 msec in adults or > 450 msec in adolescents OR a change of QTc interval > 60 msec from baseline.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis.

The study will 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, any data deriving from other clinical trials or toxicological studies that negatively influence the risk/benefit assessment may cause discontinuation or termination of the study.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

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

State of Emergency or Pandemic Related Acceptable Protocol Modifications

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

The investigator should contact the AbbVie medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure that all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix F for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

Delays in study drug dosing due to COVID-19 must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinue study drug.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they prematurely discontinue treatment with study drug.

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

Subjects who prematurely discontinue study drug, but continue study participation should complete a PD visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix D, and adhere to all study procedures except for dispensing study drug and PK sample collection. Once the subject has discontinued study drug, all rescue and efficacy driven discontinuation criteria no longer apply. If at any point a subject no longer wants to provide

assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required. The 30-Day Follow-Up visit is not applicable for subjects who discontinued study drug and continued study participation and completed at least one study visit at least 30 days after last dose of study drug.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

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 that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected, and the samples will be destroyed. Data generated for biomarker research before subject withdrawal of consent will remain part of the study results.

5.7 Treatment After End of Study

For active subjects randomized to upadacitinib, subjects will continue study treatment throughout the study for a period of up to 260 weeks or until premature discontinuation of study drug. At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject. AbbVie will not provide drug or any other therapy once the subject's participation is concluded.

5.8 Study Drug

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug and Placebo

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib (ABT-494)	oral	Film-Coated Tablet	15 mg 30 mg	AbbVie
Placebo for upadacitinib (ABT-494)	oral	Film-Coated Tablet	NA	AbbVie

NA = not applicable

Upadacitinib and matching placebo will be taken QD beginning on Day 1 (Baseline) and should be taken at approximately the same time each day. The study drug can be taken with or without food. The study drug should be taken whole and should not be split, crushed, dissolved, etc. If a subject should forget to take upadacitinib or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 10 hours before their next scheduled dose. Otherwise they should take the next dose at the next scheduled dosing time.

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

AbbVie will not supply drug other than upadacitinib or matching placebo. If a subject is unable to come to the study site to pick up their study drug due to a state of emergency or pandemic (e.g., COVID-19 pandemic), a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to Section 5.10 for details on DTP shipment of study drug.

There are no time limits for study drug interruption if no permanent study discontinuation criteria have been met.

For allowed study drug interruption due to elective and emergency surgeries, the following rules apply:

1. 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.
2. Elective surgery, and interruption of study drug for such a surgery, will not be allowed during the study until the primary endpoint has been assessed (Week 16). If the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Packaging and Labeling

Upadacitinib and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each bottle (kit) label will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the bottles (kits). All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

Storage and Disposition of Study Drug

Upadacitinib and matching placebo must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed as appropriate.

Selection and Timing of Dose for Each Subject

The study drug (upadacitinib or placebo) will be dispensed in the form of bottles with 15 mg, 30 mg, or matching placebo tablets at the visits listed in Appendix D. Subjects will be instructed to take study drug orally as 1 tablet once daily at approximately the same time each day with or without food. The study drug should be taken whole and should not be split, crushed, dissolved, etc.

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 generated by the statistics department at AbbVie. Subjects in the main study will be randomized in a 1:1:1 ratio to one of the three treatment groups:

- Group 1: Upadacitinib 15 mg (N = 270)
- Group 2: Upadacitinib 30 mg (N = 270)
- Group 3: Placebo (N = 270)

Upon completion of enrollment of 810 subjects in the main study, the adolescent sub-study will continue to enroll adolescent subjects until a total of 180 adolescent subjects are enrolled in the overall study (main study + adolescent sub-study). Subjects in the adolescent sub-study will be randomized in a 1:1:1 ratio to one of the three treatment groups:

- Group 1: Upadacitinib 15 mg
- Group 2: Upadacitinib 30 mg
- Group 3: Placebo

For the main study, randomization will be stratified by baseline disease severity (moderate [Investigator's Global Assessment (vIGA-AD) = 3] versus severe [vIGA-AD = 4] AD), by geographic region (US/Puerto Rico/Canada, Other, China, and Japan), and age (adolescent [ages 12 - 17] versus adult [ages 18 - 75]). For the adolescent sub-study, randomization will be stratified by baseline disease severity (moderate [vIGA-AD = 3] versus severe [vIGA-AD = 4]) and by geographic region (US/Puerto Rico/Canada and Other).

At Week 16 of the main study and of the adolescent sub-study, the subjects remaining in Group 3 will be re-randomized in a 1:1 ratio to one of two treatment groups:

- Group 4: Upadacitinib 15 mg
- Group 5: Upadacitinib 30 mg

For the main study, the re-randomization will be stratified by EASI 50 responder (Yes/No), by geographic region (US/Puerto Rico/Canada, China, Japan, and Other), and by age (adolescent [ages 12 to 17] versus adult [ages 18 to 75]). For the adolescent sub-study, the re-randomization will be stratified by EASI 50 responder (Yes/No) and by geographic region (US/Puerto Rico/Canada and Other).

IRT will provide the appropriate study drug kit number(s) to dispense to each subject. Returned study drug must not be re-dispensed to any subject.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the

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.

Enrollment in Japan will be capped at 45 subjects (15 subjects per group), with a target enrollment number of approximately 30 to 45 subjects (10 to 15 subjects per group).

Enrollment in China will be capped at 45 subjects (15 subjects per group), with a target enrollment number of approximately 30 to 45 subjects (10 to 15 subjects per group).

Blinding

Study sites and subjects will remain blinded for the duration of the study. To maintain integrity of the trial and avoid introduction of bias, the study team will only have access to unblinded subject level data for AEs of special interests and SAEs for regulatory submissions. In order 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 medical emergency.

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 EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/helpdesk/.

In the event that the blind is broken before notification to the AbbVie TA SD, we request that the AbbVie TA SD 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 the appropriate eCRF.

Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

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

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified, including those that may be due to a state of emergency or pandemic (e.g., 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 site.

5.10 Other Study Procedures

Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject, the benefits and risks anticipated from participation in the study, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, parent or legal guardian (for subject ≥ 12 years old and < 18 years old) the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. An assent form may need to be signed and dated for adolescent subjects, according to the country requirements. If a subject becomes of legal age during the course of the study, that subject will need to be consented using the approved informed consent form.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed because of participation in the study can be found in the informed consent form.

Optional biomarker samples will only be collected if the subject has voluntarily provided consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to optional biomarker samples, it will not impact the subject's participation in the study. In the event a subject withdraws consent to participate from the study, optional biomarker samples will continue to be stored and used for research. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

Optional photography will be performed at selected sites and only if the subject has voluntarily provided consent, approved by an IRB/IEC, after the nature of the photography sub-study has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to the optional photography sub-study, it will not impact the subject's participation in the study.

Due to a state of emergency or pandemic (e.g., COVID-19), it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

Screening and Re-Screening Procedures

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Operations Manual Section 2.1 (Appendix F). Laboratory values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a

screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

Subjects who initially screen-fail for the study are permitted to re-screen once following re-consent. For additional re-screening, AbbVie TA SD approval is required. As appropriate, sites are encouraged to contact the AbbVie TA SD to confirm if subjects should or should not be re-screened. All screening procedures with the possible exceptions noted below will be repeated during rescreening. The subject must meet all eligibility criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

If the subject had a complete initial screening evaluation including the following assessments, these tests will not be required to be repeated for re-screening, provided the conditions noted in Section 5.1, there are no changes in the subject's medical history that would warrant re-testing, and no more than 90 days have passed:

- HBV, HCV and HIV serology
- Interferon-gamma release assay (IGRA; QuantiFERON TB Gold test [or IGRA equivalent such as T SPOT test] and/or local PPD skin test, if required)
- Chest x-ray
- ECG

Subjects who are between ≥ 12 and < 18 years of age at the time of the Screening visit will be considered adolescents for the duration of the study. The age at the time of Re-Screening Visit will be used for subjects who Re-Screen.

Medical History

A complete non-AD medical history, including demographics, history of tobacco, alcohol, and nicotine use, will be taken at Screening. Additionally, a list of each subject's specific AD related medical history should be recorded at Screening. History of clinical herpes zoster, herpes zoster vaccination, and hepatitis B vaccination status will be recorded as part of the medical history.

The subject's medical history will be updated prior to study drug administration at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment and to ensure the subject is still eligible for enrollment.

A detailed medical history with respect to TB risk factors will be documented in the study source documentation. This information will include Bacillus Calmette–Guérin vaccination, cohabitation with individuals who have had TB, and travel to, residence in, or work in TB endemic locations.

In Japan, the hepatitis screen requirements are as follows:

- A positive test result for HBc Ab or HBs Ab requires HBV DNA PCR testing (automatic reflex testing).
- A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.
- A subject with a negative result for HBV DNA may be enrolled.

- For subjects with HBs Ab positive (+) and/or HBc Ab positive (+) and negative HBV DNA at Screening, HBV DNA PCR test should be performed approximately every 12 weeks (in correlation with a scheduled visit). HBV-DNA PCR testing approximately every 12 weeks is not necessary in case of subjects with history of HBV vaccine and HBs Ab positive (+) and HBc Ab negative (–).
- Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at Screening who develop a positive result for HBV DNA PCR testing during the study accompanied by the following should be referred to a hepatologist within one week for consultation and recommendation regarding subsequent treatment, and study drug interruption should be considered per local guidelines:
  - an ALT or AST > 5 × ULN OR
  - ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR
  - ALT or AST > 3 × ULN along with clinical signs of possible hepatitis.

In China, a syphilis Ab test will be performed at Screening utilizing the Toluidine Red Unheated Serum Test (TRUST) to test anticardiolipin antibody in serum. Subjects with a positive TRUST result will have a Treponema pallidum particle agglutination assay (TPPA) to confirm a syphilis infection. A positive test result for both the TRUST and TPPA tests will be exclusionary. The syphilis tests will be performed by a certified laboratory.

Drug and Alcohol History

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit. Results are reported from the subject interview.

Urine specimens will be tested at the screening visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed below. Any positive result must be assessed for clinical significance. These analyses will be performed by the certified central laboratory chosen for the study.

- Opiates
- Barbiturates
- Amphetamines
- Cocaine
- Benzodiazepines
- Alcohol
- Phencyclidine
- Propoxyphene
- Methadone

Adverse Event Assessment

The subjects will undergo physical examination for any active AEs and AEs that have occurred and resolved since the last visit as well as be interviewed for AEs that are not apparent in a physical examination. SAEs and protocol related nonserious AEs that occur after a subject signs the informed consent will be collected, prior to the first dose of study drug. Please refer to Section 6.1.

Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instrument (when allowed per local regulatory guidelines) at study visits specified in Appendix D. Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

Subjects will complete the following questionnaires below as specified in Operations Manual Section 2.1 (Appendix F). Worst Pruritus NRS, ADerm-SS daily items, ADerm-IS daily items, ADerm-SS weekly items, ADerm-IS weekly items, SCORAD, POEM, PGIS, PGIC, PGIT, DLQI, CDLQI, EQ-5D-5L, SF-36, HADS, and WPAI should be administered before any study procedures in the order listed.

A validated translation will be provided in their local language, as applicable. All PROs are collected electronically. The subject should complete the questionnaires before site personnel perform any clinical assessments and preferable before any interaction with site personnel has occurred to avoid biasing the subject's response.

The PRO instrument should be completed prior to drug administration on Day 1 and prior to any discussion of AEs or any review of laboratory findings.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to a state of emergency or pandemic (e.g., COVID-19 pandemic), subject visits may be conducted via phone or video conference. The primary site monitor will inform the site which PROs are eligible for completion by interview. In this situation, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by videoconference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

Worst Pruritus Numerical Rating Scale (NRS)

The Worst Pruritus NRS is an assessment tool that subjects used to report the intensity of their pruritus during a daily recall period. Subjects are asked the question: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst imaginable itch,' how would you rate your itch at its worst during the past 24 hours?" The Worst Pruritus NRS will be administered on electronic hand-held devices from Screening through Week 16; devices will be given to subjects to take home at Screening. Hand-held device usage

ends at the Week 16 visit. Starting at the Week 20 visit, the frequency of administration will be reduced from daily assessments to assessments only at scheduled site visits using a tablet at the site.

Atopic Dermatitis Symptom Scale (ADerm-SS)

The ADerm-SS is an 11-item PRO questionnaire designed to assess signs and symptoms that subjects may experience due to AD using a 24-hour recall period. The ADerm-SS includes three items that subjects complete daily and 8 items that subjects completed each week. The daily items include: worst itch during sleep hours, worst itch during awake hours, and worst skin pain. The 8 weekly items are also assessed using a 24-hour recall period. These items include worst skin cracking, worst pain caused by skin cracking, worst dry skin, worst skin flaking, worst rash (i.e., redness, blisters, bumpy skin), worst skin thickening, worst bleeding, and worst skin oozing. All items of the ADerm-SS are scored on an 11-point NRS ranging from 0 (no [sign/symptom concept]) to 10 (worst possible [sign/symptom concept]).

The ADerm-SS will be administered on electronic hand-held devices from Screening through Week 16; devices will be given to subjects to take home at Screening. Hand-held device usage ends at the Week 16 visit. Starting at the Week 20 visit, the frequency of administration will be reduced from daily/weekly assessments to assessments only at scheduled site visits using a tablet at the site.

Atopic Dermatitis Impact Scale (ADerm-IS)

The ADerm-IS is a 10-item PRO questionnaire designed to assess a variety of impacts that subjects experience from their AD across both a 24-hour recall period (the daily items 1 to 3) and 7-day recall period (the weekly items 4 to 10). Daily items are related to sleep, and include difficulty falling asleep, impact on sleep, and waking at night. Weekly items include household activities (e.g., washing dishes, sweeping, doing laundry), physical activities (e.g., walking, exercising), social activities, concentration, self-consciousness, embarrassment, and sadness. All items of the ADerm-IS are scored on an 11-point NRS from 0 (no impact) to 10 (extreme impact).

The ADerm-IS will be administered on electronic hand-held devices from Screening through Week 16; devices will be given to subjects to take home at Screening. Hand-held device usage ends at the Week 16 visit. Starting at the Week 20 visit, the frequency of administration will be reduced from daily/weekly assessments to assessments only at scheduled site visits using a tablet at the site.

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on quality of life (QoL). It consists of 10 questions assessing impact of skin diseases on different aspects of subject's QoL over the prior week. The DLQI items include symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a 4-point scale: 0 = not at all/not relevant; 1 = a little; 2 = a lot; and 3 = very much. Item scores (0 to 3) are added to provide a total score range of 0 to 30; higher scores indicate greater impairment of QoL. For general inflammatory skin conditions, a change in DLQI score of at least 4 points is considered the MCID. The DLQI will be administered on the tablet at site visits throughout the study. Throughout this study, the DLQI will be administered to subjects who are ≥ 16 (16 to 75) years old at the time of the Screening visit.

Children's Dermatology Life Quality Index (CDLQI)

The CDLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QoL. The CDLQI has been validated for use in subjects 4 - 16 years old. It consists of 10 questions assessing impact of skin diseases on different aspects of patient's QoL over the prior week. The CDLQI items include symptoms and feelings, daily activities, leisure, school, relationships, sleep, and treatment. Each item is scored on a 4-point scale: 0 = not at all; 1 = only a little; 2 = quite a lot; and 3 = very much. Item scores (0 to 3) are added to provide a total score range of 0 to 30; higher scores indicate greater impairment of QoL. In this study, the CDLQI will be administered to subjects who are < 16 years old at the time of the Screening visit, and will continue to be administered to these subjects for the duration of this study.

Patient-Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in both children and adults. Subjects respond to 7 items, including dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping, each scored on a 5-point scale based on frequency: 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days. Item scores (0 to 4) are added to provide a total score range of 0 to 28; the total score reflects disease-related morbidity. A change in POEM score of 3.4 points is considered the MCID. The POEM will be administered on the tablet at site visits throughout the study.

Hospital Anxiety and Depress Scale (HADS)

The HADS is a 14-item questionnaire, with seven items related to anxiety (HADS-A) and seven items related to depression (HADS-D). Each item is scored from 0 to 3; scores for each subscale range from 0 to 21 and scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. For each domain, scores 7 or lower are considered normal, 8 to 10 are borderline, and 11 or higher indicate clinical anxiety or depression. HADS will be administered on the tablet at site visits throughout the study.

Work Productivity and Activity Impairment Index: Atopic Dermatitis (WPAI:AD)

The WPAI:AD is a validated instrument used to measure loss of productivity at work and impairment in daily activities over the past 7 days. The questionnaire includes four items: absenteeism, presenteeism, overall work impairment, and activity impairment, that range from 0% to 100%, with higher values indicating greater impairment. While absenteeism represents the percentage of work time missed due to AD, presenteeism represents the percentage of impairment while at work due to AD. Overall work impairment represents the total percentage of work time missed due to either absenteeism or presenteeism (since those are mutually exclusive). Activity impairment represents the percentage of impairment during daily activities other than work. The 4 items are all evaluated using an 11-point Likert-type scale from 0 (no effect) to 10 (completely prevented), and the scores are multiplied by ten to arrive at a percentage.

The WPAI:AD will be administered on the tablet at site visits throughout the study.

EuroQoL Dimensions 5 Levels (EQ-5D-5L)

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists

of 2 parts: the descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement (i.e., no problems, some problems, or severe problems) in each of the 5 dimensions; this results in a 1-digit number expressing the level for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled "best imaginable health state (100)" and "worst imaginable health state (0)." This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The EQ-5D-5L will be administered on the tablet at site visits throughout the study.

Patient Global Impression of Severity (PGIS)

The PGIS asks subjects to describe the severity of their AD symptoms right now. Subjects rate their AD symptoms on a 7-point scale ranging from 0 = Absent (no symptoms) to 6 = Very Severe (cannot be ignored and markedly limits my daily activities).

The PGIS will be administered on the tablet at site visits throughout the study.

Patient Global Impression of Change (PGIC)

The PGIC asks subjects to rate the overall change in their AD symptoms by comparing the severity of their AD symptoms right now with the severity of their AD symptoms before they began study treatment. Subjects are asked: "Compared to before your study treatment began, how would you rate the overall change in your atopic dermatitis symptoms?" Responses range from 1 = "Very much improved" to 7 = "Very much worse."

The PGIC will be administered on the tablet at site visits throughout the study. The PGIC will not be collected at Baseline.

Patient Global Impression of Treatment (PGIT)

The PGIT asks subjects to rate their level of satisfaction/dissatisfaction with their current treatment for AD. Subjects are asked: "Overall, how satisfied or dissatisfied are you with your current treatment for atopic dermatitis?" Responses range from 1 = "Extremely dissatisfied" to 7 = "Extremely satisfied."

The PGIT will be administered on the tablet at site visits throughout the study.

Short Form-36 Health Survey (SF-36)

The SF-36 Health Survey is a generic assessment that measures general health status. The SF-36 includes eight domains rated over the prior four weeks: physical function, role limitations – physical, bodily pain, general health perceptions, vitality, social function, and role limitations with regard to emotional and mental health. Two component scores, the Physical Component Summary and the Mental Component Summary (MCS) are calculated. The SF-36 domain and summary scores are

transformed to a normative scale with a mean of 50 and standard deviation of 10, with higher scores indicating better physical function or well-being.

The SF-36 will be administered on the tablet at site visits throughout the study.

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD. There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the subject or relative on a VAS on the tablet, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C where the maximum is 103.

The SCORAD subjective symptoms (component C) will be administered on the tablet at site visits throughout the study. SCORAD components A and B will not be on the tablet and performed on paper worksheets and entered into the electronic case report form (eCRF). The rule of 9's method should be used to assess the percentage of each defined body area on the paper worksheets for component A.

Investigator Assessment

The investigator assessments will be recorded on paper worksheets and entered into the eCRF and conducted at the study visits specified in Appendix D. If possible, the investigator assessments should be performed by an independent and blinded assessor who should not perform any other study related procedures. In order to minimize variability, the same independent assessor should evaluate the subject at each visit for the duration of the study. A back-up independent assessor should be identified. The independent assessor must be a qualified medical professional (e.g., nurse, physician's assistant, or physician). Any assessor must be trained and competent in performing such assessments. It is the responsibility of the investigator to ensure that all assessors are qualified and trained to perform assessments and that all training is documented. If the independent assessor is not available, the pre-identified back-up assessor should perform such assessments.

Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD)

The vIGA-AD is a validated assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe).

Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the investigator or designee on a scale of "0"

(absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk (including the genital area), upper extremities, and lower extremities (including the buttocks), and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

Body Surface Area Involvement of Atopic Dermatitis (BSA, %)

A qualified investigator or designee should select the subject's right or left hand as the measuring device. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1%. Measurement of the total area of involvement by the investigator is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved. The site should make every attempt to have the same qualified investigator or designee perform all BSA assessments on a given subject throughout the study.

SCORing Atopic Dermatitis (SCORAD)

See description above in Patient-Report Outcomes.

Hand eczema severity index (HECSI)

Each hand is divided into five areas [fingertips, fingers (except the tips), palms, back of hands and wrists]. For each of these areas the intensity of the six following clinical signs: erythema, induration/papulation, vesicles, fissuring, scaling and edema is graded on the following scale: 0, no skin changes; 1, mild disease; 2, moderate and 3, severe. For each location (total of both hands) the affected area is given a score from 0 to 4 (0, 0%; 1, 1 – 25%; 2, 26 – 50%; 3, 51 – 75% and 4, 76 – 100%) for the extent of clinical symptoms. Finally, the score given for the extent at each location is multiplied by the total sum of the intensity of each clinical feature, and the total sum called the HECSI score is calculated, varying from 0 to a maximum severity score of 360 points.

None of the investigator assessments described above (vIGA-AD, EASI, BSA, SCORAD and HECSI) can be performed remotely, as they require in-person evaluation of the skin.

Vaccines

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid, or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (tetanus-diphtheria-acellular pertussis).

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

In Japan, it is recommended that the live herpes zoster vaccine should be considered for administration at least 8 weeks before first dose of study drug or administered at least 30 days after last dose of study drug.

See Section 5.3 for a list of commonly used live vaccines that are prohibited during study participation.

Tuberculosis Testing

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the investigator to determine if a subject has previous, active, or latent TB.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form (Operations Manual Section 3.18 [Appendix F]) and tested for TB infection (QuantiFERON TB Gold test [or IGRA equivalent such as T-SPOT test] and/or local PPD skin test, if required) as described below. The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF. The TB risk factor questionnaire will be done at Week 52 and annually after Week 52, regardless of TB test results.

If a subject had a negative PPD test within 90 days prior to Screening and a QuantiFERON-TB Gold test (or IGRA equivalent such as T-SPOT test) cannot be performed at Screening and source documentation is available, TB testing by PPD skin test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TA SD. The results of the TB test(s) will be retained at the site as the original source documentation.

Subjects with a negative TB test and chest x-ray not suggestive of active TB or prior TB exposure may be enrolled.

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and chest x-ray. Subjects with no signs or symptoms and a chest x-ray not suggestive of active TB may be enrolled after initiation of TB prophylaxis (see below).

Subjects with evidence of active TB must not be enrolled.

For subjects with a negative TB test result at Screening or the most recent evaluation, an annual TB follow-up test will be performed. In cases where the annual QuantiFERON-TB Gold test by the central laboratory is positive and the investigator considers the subject at low risk for TB (i.e., no risk factors identified using the TB risk assessment form) and has no clinical suspicion of TB, the investigator may perform a QuantiFERON TB gold test at a local lab (or through the central laboratory if not locally available) to confirm the positive test result: if repeat testing result is negative, then the investigator may consider the subject to be negative based on his/her clinical judgment; if repeat testing result is positive, then the subject is considered to be positive.

The annual TB test can be completed at the earliest feasible opportunity if not able to be completed per protocol schedule due to a state of emergency or pandemic restrictions. If an annual TB test is newly positive (seroconversion), a chest x-ray needs to be performed as soon as possible to aid in distinguishing active versus latent TB, and subsequent annual TB follow-up tests are not required. Any positive TB test after the subject has started the study, should be reported as an AE of latent TB or active TB (as applicable).

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant a repeat test before the next scheduled annual TB re-test, the case (including the TB test results) must be discussed with the AbbVie TA MD.

TB test

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold test (or IGRA equivalent such as T-SPOT TB test) and/or PPD are not required to repeat either test at Screening or during the study and should be considered positive.
- For regions that require both PPD and QuantiFERON-TB Gold testing (or IGRA equivalent, such as T-SPOT TB test), both will be performed. If either PPD or QuantiFERON-TB Gold (or IGRA equivalent, such as T-SPOT TB test) is positive, the TB test is considered positive.
- The PPD Skin Test (also known as a TB Skin Test or Mantoux Test) should be utilized only when a QuantiFERON-TB Gold test (or IGRA equivalent, such as T-SPOT TB test) is not possible for any reason (unless both tests are required per local guidelines).
- If only a PPD is placed at Screening, then the TB test to be used for the remainder of the study for that subject is the PPD. Similarly, if a subject enters the study with a QuantiFERON-TB Gold Test (or IGRA equivalent, such as T-SPOT TB test) alone, then the subject should have their annual TB test performed with a QuantiFERON-TB Gold Test (or IGRA equivalent, such as T-SPOT TB test).
- If the QuantiFERON-TB Gold test (or IGRA equivalent, such as T-SPOT TB test) is NOT possible (or if both the QuantiFERON-TB Gold test (or IGRA equivalent, such as T-SPOT TB test) and the PPD are required per local guidelines) the PPD will be performed. The PPD should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have an ulcerating reaction to the PPD in the past should not be re-exposed and the PPD should be considered positive.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a QuantiFERON TB gold test at a local lab (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the subject is considered to be negative.

TB prophylaxis

At Screening, if the subject has evidence of latent TB infection, prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer); at least 6 months of prophylaxis need to be completed, however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Of note: Rifampicin or rifapentine is not allowed for TB prophylaxis.

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment. For subjects with completion of a full course of anti-TB therapy, but insufficient documentation, the investigator should consult with the AbbVie TA MD.

During the study, subjects with new evidence of latent TB must initiate prophylactic treatment immediately per local guidelines and complete at least 6 months of prophylaxis. Study drug(s) should not be withheld. Two to 4 weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms as well as laboratory assessment of toxicity to TB prophylaxis.

Newly initiated prophylactic treatment and prior therapy should be captured in the eCRF.

Chest X-Ray

A chest x-ray (posterior-anterior and lateral views) is required:

- For all subjects at Screening to rule out the presence of TB or other clinically relevant findings. The screening CXR will not be required if the subject had a previous normal CXR (posterior-anterior and lateral views) within 90 days of Screening, provided all source documentation is available at the site, as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test.
- At Week 52, and annually thereafter, for subjects with newly identified TB risk factors as identified by the TB risk assessment form (Operations Manual Section 3.18 [Appendix F]), or for subjects living in areas endemic for TB or for subjects with newly positive PPD and/or QuantiFERON-TB Gold test (or IGRA equivalent, such as T-SPOT TB test). The chest x-ray can be completed at the earliest feasible opportunity if not able to be completed per protocol schedule due to state of emergency or pandemic (e.g., COVID-19 pandemic) restrictions.

Subjects can have a repeat chest x-ray at any time during the study as warranted based on the opinion of the investigator. A radiologist or pulmonologist must perform and document an assessment of the chest x-ray. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the chest x-ray, the Principal Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the chest x-ray demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator should contact the AbbVie TA MD before enrolling the subject.

12-Lead Electrocardiogram

A 12-lead ECG will be performed at the designated study visits as specified in Appendix D. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Height and Body Weight

Height and body weight will be measured without shoes at visits specified in Appendix D. Weight will be performed throughout the study for all subjects (both adults and adolescents). For adults, collection of height will be at the Baseline Visit only. For adolescent subjects (subjects who were 12 to 17 years of age at Screening Visit), collection of height will be at the Screening and Baseline Visits and designated visits thereafter. All measurements will be recorded in imperial or metric units where applicable.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to a state of emergency or pandemic (e.g., COVID-19 pandemic), perform the 12-lead ECG at the next earliest feasible visit.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Appendix D. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Appendix D. The physical examination at the Baseline Visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted by the investigator at baseline prior to the first dose of study drug will be recorded in the subject's medical history; abnormalities noted after the first dose of study drug will be evaluated and documented by the investigator as to whether or not the abnormality is an AE. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

Tanner Staging

The Tanner Scale (also known as the Tanner Stages) is a validated measure used in clinical practice and clinical trials to assess physical development (Operations Manual Section 3.19 [Appendix F]). The Scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitals, testicular volume and development of pubic hair.

Throughout this study, Tanner Staging will be assessed at Baseline for subjects who are < 18 (12 to 17) years old at the time of the Screening Visit, and will continue to be assessed for these subjects for the duration of this study. Once a subject reaches stage 5 in both categories, Tanner Staging will no longer need to be assessed for that subject.

Dispense Study Drug

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Appendix D. The first dose of study drug will be administered after all other screening procedures are completed.

Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

Subjects will be instructed to take study drug orally as 1 tablet once daily at approximately the same time each day with or without food.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- DTP shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
- At the Week 16 and 20 visits, or at any visit wherein the subject has previous lab abnormalities that required follow-up, study drug cannot be dispensed without labs being obtained. At all other visits, study drug can be dispensed if labs have been obtained within the prior 3 months until Week 124 and within the prior 6 months between Week 124 and Week 260 and as long as the investigator has determined that it would be safe for the subject to continue to receive study treatment.
    - Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of PROs). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Clinical Laboratory Tests

Blood and urine samples will be collected at the designated study visits as specified in Appendix D and following a minimum 8-hour fast. If a subject is not able to fast when necessary (except during Screening visit), due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution.

A laboratory test value that requires a subject to be discontinued from the study drug or requires a subject to receive treatment will be recorded as an AE. The central laboratory chosen for this study will provide instructions regarding the collection, processing and shipping of these samples. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr><td>Hematocrit
Hemoglobin
RBC count
WBC count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count</td><td rowspan="2">BUN
Creatinine
Total bilirubin
INR (reflex only)[a]
Albumin
ALT
AST
Alkaline phosphatase
CPK
Sodium
Potassium
Bicarbonate/CO_2
Chloride
Calcium
Inorganic phosphorus
Uric acid
Total protein
Glucose
Cholesterol
LDL-C
HDL-C
Triglycerides</td><td rowspan="2">Central Lab Tests:
Serum pregnancy (bHCG) test
HBs Ag
HBs Ab
HBc Ab
HBV DNA PCR reflex only
HCV Ab
HCV RNA reflex only
HIV Ab
QuantiFERON-TB Gold test
hs-CRP
FSH[b]
Total IgE
Urine drug screen

Local Lab Tests:
Urine pregnancy test
IGRA equivalent such as T-SPOT test if central QuantiFERON-TB Gold test not done</td></tr>
<tr><th>Urinalysis</th></tr>
<tr><td>Specific gravity
Ketones
pH
Protein
Blood
Glucose
Urobilinogen
Bilirubin
Leukocytes
Nitrites
Microscopic examination, if needed</td></tr>
</table>

Ab = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bHCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CO_2 = carbon dioxide; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; FSH = Follicle-Stimulating Hormone; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; IGRA = interferon-gamma release assay; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; PCR = polymerase chain reaction; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell

a. INR will only be measured if ALT and/or AST > 3 × upper limit of normal (ULN).

b. At screening only for female ≤ 55 years old.

Serum Pregnancy Test

A serum pregnancy test will be performed for females of childbearing potential at the Screening Visit. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility. If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure or should be discontinued from study;
- Negative, the subject can be enrolled into the trial or continue in the study;

- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study or continue in the study (unless prohibited locally/country requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Urine Pregnancy Test

A urine pregnancy test will be performed locally for all females of childbearing potential at the Baseline Visit prior to the first dose of study drug and at minimum at monthly intervals (either at study visits or at home between scheduled study visits). The results of the monthly at home tests must be communicated to the site. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

- If the Baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin.
- If the Baseline or post-baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started or resumed. If the serum pregnancy test is positive, study drug must be permanently discontinued. In the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later). If the repeat serum pregnancy test is:
  - Positive, the subject is considered a screen failure or should be discontinued from study drug;
  - Negative, the subject can be enrolled into the trial or continue on study drug;
  - Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study or continue in the study (unless prohibited locally/country requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

If time between visits is longer than 1 month, then collect the results of the monthly at home urine pregnancy test between scheduled visits.

If during the course of the study a female becomes surgically sterile or postmenopausal and complete documentation as described in Section 5.2 (Contraception Requirements for Females) is available, pregnancy testing is no longer required.

A pregnant or breastfeeding female will not be eligible to enter the study or be allowed to continue study drug.

High-sensitivity C Reactive Protein (hsCRP)

The hsCRP results will remain blinded to the Sponsor, investigator, study site personnel, and subject for all visits except Screening. Investigators should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigators should also refrain from locally testing procalcitonin except for safety evaluations of signs and symptoms of infection or AEs.

Clinical Chemistry

A minimum 8-hour fast will be necessary for blood samples to be drawn for chemistry. If a subject is not able to fast when necessary due to unforeseen circumstances, the nonfasting status will be recorded in study source documentation.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

Hepatitis Screen

All subjects will be tested for the presence of HBV and HCV at screening.

Hepatitis B Virus

Subjects will be tested for the presence of HBV at screening using the following tests:

- HBs Ag
- HBc Ab/HBc
- HBs Ab/HBs

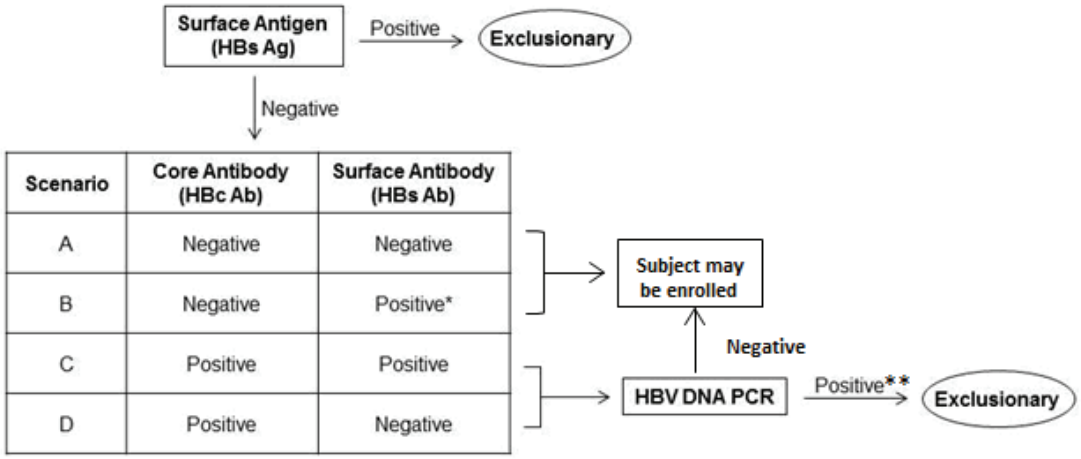
A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will be tested (automatic reflex testing) for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

- A negative test result for HBc Ab does not require HBV DNA polymerase chain reaction (PCR) qualitative testing and the subject may be enrolled (Figure 2, Scenarios A and B).
- For a subject who has had an HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected and the subject may be enrolled (Figure 2, Scenario B).*
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 2, Scenarios C and D).
  - A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.
  - A subject with a negative result for HBV DNA testing may be enrolled.
- Where mandated by local requirements: A positive result for HBs Ab requires HBV DNA PCR testing.
  - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.

- For subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening, HBV DNA PCR test should be performed approximately every 12 weeks (in correlation with a scheduled visit). HBV DNA PCR testing approximately every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+, HBc Ab–.
- Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop a positive result for HBV DNA PCR testing during the study accompanied by the following should be referred to a hepatologist within one week for consultation and recommendation regarding subsequent treatment, and immediate study drug interruption will be required (or per local guidelines):
  - an ALT > 5 × ULN OR
  - ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or INR > 1.5 OR
  - ALT or AST > 3 × ULN along with clinical signs of possible hepatitis.

Figure 2. Interpretation and Management of HBV Serologic Test Results



DNA = deoxyribonucleic acid; HBc Ab = hepatitis B core antibodies; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction

* A positive test result for HBs Ab is expected for subjects who have had an HBV vaccination. For subjects without a history of HBV vaccination (and for subjects in Japan and China or where mandated by local requirements) a positive result for HBs Ab/anti-HBs requires HBV DNA PCR testing.

** Where mandated by local requirements; subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed approximately every 12 weeks (in correlation with a scheduled visit). HBV DNA PCR testing approximately every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–.

Hepatitis C Virus (HCV)

Blood samples for HCV serology will be obtained at the Screening Visit. A positive HCV Ab (antibody) will trigger an HCV RNA test. A subject will not be eligible for study participation if test results indicate active Hepatitis C (HCV RNA detectable in any subject with anti HCV Ab).

Human Immunodeficiency Virus (HIV)

Subjects with HIV infection (positive HIV test) are excluded from study participation. HIV testing will be performed at Screening, unless prohibited by local regulations. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. This testing is to be done at the central lab. AbbVie will not receive results from the testing and will not be made aware of any positive result.

TBNK Assessment By Immunophenotyping

Blood samples will be utilized to assess effects of Janus kinase inhibition on certain leukocyte subsets, including T (CD4+ and CD8+) cells, B (CD19+) cells, natural killer (NK) cells, and natural killer-T (NKT) cells. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of a state of emergency or pandemic (e.g., COVID-19 pandemic) prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs (also refer to section "Dispense Study Drug"). The subject should be scheduled for laboratory draws as soon as feasible within the protocol defined visit window from the scheduled visit, as described in Section 2.1 of the Operations Manual (Appendix F).

Discontinuation of Study Drug and Subject Withdrawal from the Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the subject decides to continue participation in the study.

Discontinuation of Study Drug and Continuation of Study Participation

During the study, subjects may discontinue study drug treatment but may choose to continue to participate in the study. Subjects who prematurely discontinue study drug should complete a Premature Discontinuation visit (PD visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Operations Manual Section 2.1 (Appendix F) and Protocol Appendix D, and adhere to all study procedures except for dispensing study drug and PK sample collection, and blood sample collection for optional exploratory research and validation studies.

As the subject has discontinued study drug, all rescue and efficacy driven discontinuation criteria may no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time. If a subject prematurely discontinues study drug treatment AND study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, if the subject is willing, a 30-day follow-up visit may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition.

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

Follow-Up Visit

A Follow-Up Visit will occur approximately 30 days after the last dose of study drug to obtain information on any new or ongoing AE/SAEs and concomitant medications. Subjects will complete the Follow-Up Visit when they have either.

- Completed the last study visit while are still on treatment; OR
- Prematurely discontinued study drug and/or study participation and have completed a PD visit.

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

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Subjects may be offered the option of home healthcare visits provided by a study nurse or third-party vendor. Study procedures conducted in the home setting may include those detailed in Section 2.1 of the Operations Manual (Appendix F) and the collection of blood samples for central or local lab testing. This option can only be offered in countries and sites that comply with local regulatory and IRB/IEC requirements for homecare. Any pre-requisite submissions or notifications to the site IRB/IEC and local competent health authority should be made, and approvals must be obtained prior to implementation. The investigator should be available via phone call if a consultation is necessary.

It is recommended that medical personnel entering a subject's home adhere to local health regulations during a pandemic (e.g., COVID-19 pandemic), such as the use of Personal Protective Equipment (PPE), as required.

Protocol deviations must be recorded per AbbVie's standard process.

Sites may collect blood samples for central or local lab testing after the following requirements are met:

1. Submission and approval of home healthcare collections of blood samples from local competent health authority and IRB/IEC, as applicable
2. Confirmation that the subject's written consent to home healthcare has been obtained

If the home visits will not be performed by site personnel, the site may be responsible for selecting a vendor, contracting with a vendor, and for ensuring continued compliance with the terms of the Clinical Study Agreement.

Individuals performing home visits need to be added to the delegation log. The Principal Investigator must ensure that any staff collecting blood samples are qualified and trained to do so per local regulations.

Pharmacokinetic Sampling

Collection of Samples for Analysis

Blood samples for the analysis of upadacitinib plasma concentrations will be collected from subjects at select sites throughout the treatment period on the study days and time points specified in Appendix D.

At Week 2 and Week 8 visits, PK samples should be collected prior to dosing and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample will be collected at any time during the visit.

For all PK samples, the date and accurate time of the PK sample collection will be recorded on the lab requisition form. The date and accurate time the last two study drug doses will be recorded on the eCRF to the nearest minute.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

Measurement Method

Plasma concentrations of upadacitinib will be determined by the Bioanalysis Department at AbbVie using a validated liquid chromatography/mass spectrometry method.

Photography Sub-Study

The photography sub-study will be done only at selected sites. During the screening visit, subjects will be asked to consent to participate in the photography sub-study. The subjects that provide a signed and dated written informed consent will be asked to have photographs taken of their disease response during the study. Photographs will be taken during the Baseline, Week 2, Week 4 and Week 16 visits.

Sites will submit the digital images to the centralized photography service. The cameras for the photographs will be standardized and supplied to the sites by a central photography service. The

photography data on the server will be considered source; and maintained and managed by the vendor. Training and detailed instructions will be provided by the central photography service.

Biomarker Samples

Optional biomarker samples (whole blood) will be collected at visits detailed in Appendix D. All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. Samples will be retained while research on upadacitinib (or drugs of this class) or AD and related conditions continues, but for no longer than 20 years after study completion, or per local requirement. Based on the value of different technologies, samples may also be used to assess other biomarker signatures, including but not limited to epigenetic, metabolomics, lipidomics, and other applications.

The results from these analyses are exploratory in nature and may not be included with the clinical study report.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Product Complaint

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

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

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

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject 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 accidental or intentional overdose, drug abuse, or drug withdrawal. 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 drug, 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 the surgery/procedure has been pre-planned prior to study entry. Elective surgery will not be allowed during the study until the primary endpoint has been assessed. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following events are reported, then the following supplemental form must be completed.

Adverse Event	Supplemental Form
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Venous thromboembolism**	Cardiovascular (Cardiac) AE eCRF Myocardial Infarction and Unstable Angina AE eCRF Heart Failure Adverse Event eCRF Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF Embolic and Thrombotic Event (Non-Cardiac, Non-central nervous system [CNS]) eCRF
Herpes Zoster Infection	Herpes Zoster AE eCRF
ALT/AST > 3 ULN	Hepatic Abnormal Laboratory Value Supplemental eCRF Hepatic Supplemental Local Labs eCRF (if applicable) Hepatic Supplemental Procedure eCRF (if applicable)
Serum creatinine > 1.5 × the baseline value and > ULN **Serum creatinine ≥ 2.0 mg/dL**	Renal Abnormal Laboratory Value Supplemental eCRF Renal Supplemental Local Labs eCRF (if applicable) Renal Supplemental Procedure eCRF (if applicable)
Creatine kinase (CPK) value ≥ 4 × ULN and no symptoms suggestive of myositis or rhabdomyolysis **CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis** **CPK increases considered by the investigator to be an AE**	Increased CPK Supplemental eCRF
Acne	Acne eCRF
Death	Death eCRF
Eczema herpeticum (or the synonymous Kaposi's varicelliform eruption)	Eczema herpeticum eCRF

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of a state of emergency or pandemic (e.g., COVID-19) related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/ Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

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

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

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

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions reporting for the Investigational Medicinal Product in accordance with global and local requirements.

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

Adverse Events of Special Interest

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

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

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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 activities of daily living (ADL)

Severe (Grade 3 - 5)

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

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

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

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

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

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

Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5).

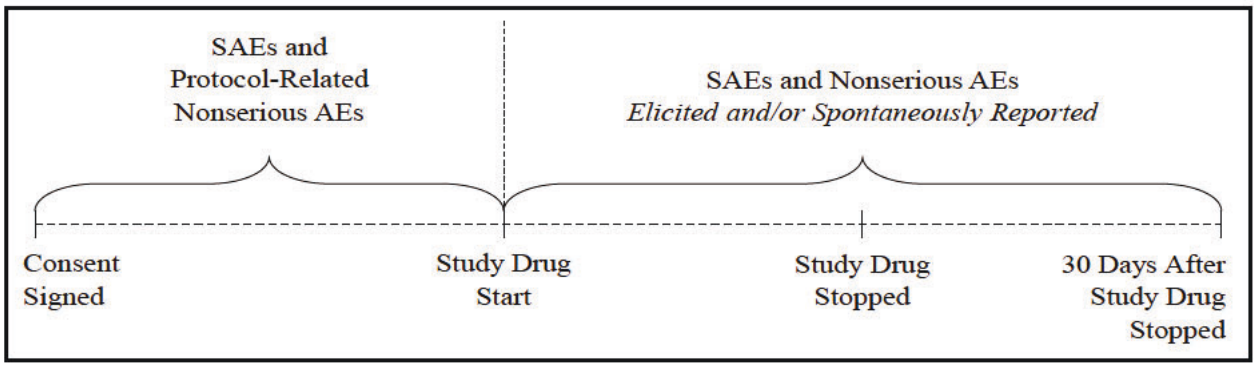
Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an AE. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Methods and Timing of Safety Assessment

All SAEs as well as protocol-related nonserious AEs will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days after discontinuation of study treatment, all nonserious AEs and SAEs will

be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected) while study is still ongoing.



Additionally, in order to assist the adjudication process, additional information on any potential Major adverse cardiovascular event will be collected, if applicable.

Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture RAVE® system. SAEs that occur prior to the site having access to the RAVE system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Safety Team at:

Therapeutic Area Safety Team
1 North Waukegan Road North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_TA@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT
[redacted]
AbbVie Inc.
1 North Waukegan Road
[redacted]
North Chicago, IL 60064

Contact Information:

Mobile: [redacted]
Email:

In emergency situations involving study subjects when the primary TA SD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA SD:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

In Japan, the principal investigator will provide documentation of all SAEs to the Director of the investigative site and the Sponsor.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described below. This includes AEs of serious infections, opportunistic infections, GI perforations, cardiovascular events (MACE), thromboembolic events, malignancies, and ECG abnormalities. This also includes the following laboratory abnormalities: hemoglobin, absolute neutrophil count, absolute lymphocyte counts, total white blood cell count, platelet count, ALT or AST, serum creatinine, and CPK. Toxicity management consists of safety monitoring (review of AEs on an ongoing basis, and periodical/ad hoc review of safety issues by a safety data monitoring committee), interruption of study drug dosing with appropriate clinical management if applicable, and discontinuation of the subjects from the study drug.

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

All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

Management of Serious Infections

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

Management of Herpes Zoster

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

Management of Serious Gastrointestinal Events

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 gastrointestinal tract that requires inpatient medical care or urgent surgical intervention (except for appendicitis or mechanical injury) must be permanently discontinued from study drug.

Management of Thrombosis Events

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

Management of Malignancy

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

Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Management of 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 ECG Abnormality

Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug, OR a confirmed absolute QTcF value > 500 msec or > 450 msec in adolescents, OR a change of QTc interval > 60 msec from baseline.

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 (see Section 6.1 [Complaints and Adverse Events]). All abnormal laboratory tests

that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 3, the repeat testing must occur as soon as possible.

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 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.
Absolute neutrophil count (ANC)	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its 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.
Absolute lymphocyte counts (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 white blood cell count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its baseline value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

Laboratory Parameter	Toxicity Management Guideline

AST or ALT	• Interrupt study drug immediately 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 > 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).
	• If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD.
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	For subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at screening who develop the following should have HBV DNA by PCR testing performed within 1 week (based on initial elevated value):
	  • ALT > 5 × ULN OR;
	  • ALT or AST > 3 × ULN if an alternate 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. As with INR, a separate tube is needed.
	A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	If serum creatinine is > 1.5 × the baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × baseline value and ≤ ULN. For this serum creatinine elevation scenario, complete the appropriate supplemental renal eCRF(s).
Creatine Phosphokinase	• If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. For the above CPK elevation scenarios, complete supplemental increased CPK eCRF.

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

6.3 Data Monitoring Committee and Cardiovascular Adjudication Committee

An external DMC comprised of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety and if necessary, efficacy data from the ongoing study. The DMC members consist of two clinicians and one biostatistician with one clinician being an expert in the management of subjects with AD. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

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

Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

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

6.4 Other Safety Data Collection

Specific manifestations of AD (i.e., itching, excoriations, oozing, crusting, erythema, etc.) should not be reported as individual AEs if they are considered to be a worsening of the underlying disease; instead, worsening of atopic dermatitis should be reported as the AE.

6.5 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a Development Safety Update Report (DSUR) reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The objective of the statistical analyses is to evaluate the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy.

For ease of description, the DB Period refers to Week 0 to 16, and the Blinded Extension Period refers to the rest of the study.

The Primary Analysis of the main study for all efficacy endpoints pertaining to the DB Period (including the primary efficacy endpoints) will be conducted after all continuing subjects in the main study have completed the study activities up to Week 16 and all data pertaining to the DB Period are cleaned. This is the one and final efficacy analysis for the DB Period of the main study. After the Primary Analysis of the main study, an additional analysis of the main study will be conducted when the required safety exposure target is reached. In addition, a Week 52 analysis of the main study will be performed after all ongoing subjects complete the Week 52 visit. Furthermore, the Primary Analysis for the adolescent population (including the adolescent subjects from the main study and the adolescent sub-study) will be conducted after all ongoing adolescent subjects have completed Week 16, and all data pertaining to the DB Period are cleaned. An additional analysis of the adolescent population will be conducted after all ongoing adolescent subjects have provided at least 1 year of upadacitinib exposure. Interim database locks may be performed after all subjects (main study and adolescent sub-study) have completed the study activities up to the relevant timepoints after Week 140. The Type-I error control will be applied to the Primary Analysis of the main study. Study sites and subjects will remain blinded for the duration of the entire study.

The statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the blind break and database lock for the Primary Analysis. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

Intent-to-Treat (ITT) Populations:

- The ITT Population (ITT) consists of all subjects who are randomized in the overall study.

- The ITT Population for the main study (ITT_M) consists of all subjects who are randomized in the main study.
- The ITT Population for adolescents (ITT_A) consists of all adolescent subjects who are randomized in the main study or the adolescent sub-study.

Subjects who are randomized to placebo in the DB Period and do not continue into the Blinded Extension Period will be excluded from the analysis in the Blinded Extension Period.

The ITT populations will be used for efficacy analyses. Subjects will be analyzed according to treatment as randomized.

Per Protocol Population:

A Per-Protocol Population for the main study (PP_M) will be defined to exclude subjects with major protocol violations. The criteria to define the Per-protocol Population will be detailed in the SAP. Subjects to be excluded from the Per-Protocol Population will be finalized before database lock and blind break. The PP_M Population will be used to analyze the primary efficacy endpoint.

Safety Populations:

- The Safety Population in the DB Period (Safety_DB) consists of all randomized subjects who received at least 1 dose of study drug in the overall study during the DB Period.
- The Safety Population in the Blinded Extension Period (Safety_BE) consists of all randomized subjects who received at least 1 dose of study drug in the overall study during the Blinded Extension Period.
- The Safety Population for the main study in the DB Period (Safety_DB_M) consists of all randomized subjects who received at least 1 dose of study drug in the main study during the DB Period.
- The Safety Population for the main study in the Blinded Extension Period (Safety_BE_M) consists of all randomized subjects who received at least 1 dose of study drug in the main study during the Blinded Extension Period.
- The Safety Population for adolescents in the DB Period (Safety_DB_A) consists of all randomized adolescent subjects who received at least 1 dose of study drug in the main study or the adolescent sub-study during the DB Period.
- The Safety Population for adolescents in the Blinded Extension Period (Safety_BE_A) consists of all randomized adolescent subjects who received at least 1 dose of study drug in the main study or the adolescent sub-study during the Blinded Extension Period.

In all safety analyses, subjects will be analyzed according to treatment received regardless of randomization.

Cross-period summaries will be provided for subjects initially randomized to the two upadacitinib groups.

In addition, the following populations will provide comprehensive summaries:

- The All Upadacitinib Treated Population (ALL_UPA) consists of all subjects who received at least 1 dose of upadacitinib in the overall study.
- The All Upadacitinib Treated Population for the main study (ALL_UPA_M) consists of all subjects who received at least 1 dose of upadacitinib in the main study.
- The All Upadacitinib Treated Population for adolescents (ALL_UPA_A) consists of all adolescent subjects who received at least 1 dose of upadacitinib in the main study or the adolescent sub-study.

7.3 Statistical Analyses for Efficacy

The efficacy analysis of the main study will be conducted in the ITT_M Population. The efficacy analysis for adolescents will be conducted in the ITT_A Population. In addition, the primary efficacy endpoints will be analyzed in the PP_M Population. Subjects will be included in the treatment group to which they are randomized.

In the DB Period, categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by vIGA-AD categories and age (adolescent vs. adult) in the ITT_M Population, and stratified by vIGA-AD categories and study portion (main study vs. adolescent sub-study) in ITT_A Population. Continuous variables will be analyzed using mixed-effect model with repeated measures (MMRM).

In the DB Period, missing values and visits after the rescue will be handled by non-responder imputation (NRI) for categorical variables or MMRM for continuous variables.

Assessments of long-term efficacy (across the DB and Blinded Extension Periods) for subjects who stay on treatment will be summarized by Observed Case approach at each visit. No missing data imputation will be applied, and all assessments prior to premature discontinuation from study drug will be used. For selected efficacy endpoints (e.g., EASI 75), long-term efficacy analysis will be performed using multiple imputation (MI).

Primary Analysis of Efficacy

The co-primary endpoints for the efficacy are:

- Proportion of subjects achieving at least an EASI 75 from Baseline at Week 16;
- Proportion of subjects achieving vIGA-AD of 0 or 1 with at least two grades of reduction from Baseline at Week 16.

Comparison of the primary endpoints will be made between each upadacitinib group and the placebo group in ITT_M Population using the CMH test, adjusting for vIGA-AD categories and age (adolescent vs. adult). NRI will be the primary approach, with MI and tipping point analysis as the sensitivity approach to handle missing values. The primary endpoints will also be evaluated in the PP_M Population.

Sample Size Estimation

Approximately 810 adolescent and adult subjects will be randomized to upadacitinib 30 mg, upadacitinib 15 mg, or placebo in a ratio of 1:1:1 in the main study (270 subjects per treatment group). The sample

size is determined by the regulatory requirement to adequately characterize the safety profile. Assuming an EASI 75 response rate of 15%, and vIGA-AD 0 or 1 with at least a 2-point reduction response rate of 10% in the placebo arm, this sample size will also provide more than 90% power to detect the treatment differences of 32% and 21%, respectively, for the above two endpoints simultaneously using two-sided test at a 0.05 significant level. The assumptions of placebo response rates for EASI 75 and IGA-AD 0/1 were based on the maximum placebo rate in upadacitinib AD Phase 2b study and dupilumab Phase 3 monotherapy studies (SOLO 1 and SOLO 2). The graphic approach for controlling multiplicity will be outlined in the Statistical Analysis Plan.

Additional adolescent subjects will be enrolled in the adolescent sub-study and randomized to upadacitinib 15 mg, upadacitinib 30 mg, or placebo in a ratio of 1:1:1 for a total of 180 adolescent subjects in the overall study (main study + adolescent sub-study). This sample size was determined to ensure a total of 225 subjects per dose across 3 pivotal studies will provide 1 year of data.

7.4 Statistical Analyses for Safety

The safety analyses will be carried out using the safety populations in the DB Period, the Blinded Extension Period, and across both periods, and will be based on treatments the subjects actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, and vital signs. Note that missing safety data will not be imputed. Analysis details will be specified in the SAP.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as those that began or worsened in severity after the first dose of study drug but within 30 days after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA system organ class (SOC) and preferred term (PT), 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, AEs leading to discontinuation and AESIs will be provided as well. Pre-treatment AEs will be summarized separately.

For laboratory and vital signs, mean change from Baseline and percentage of subjects with evaluations meeting criteria for pre-defined Potentially Clinically Significant values will be summarized.

7.5 Pharmacokinetic and Exposure-Response Analyses

Individual upadacitinib plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods.

Data from this study may be combined with data from other studies for the population PK and exposure-response analyses. Population PK and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population PK and exposure-response analyses.

Population PK analyses (using the available PK data from the subjects from whom the PK samples will be collected) will be performed using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling approach with non-linear mixed effects modeling software (Version 7, or a higher version). The structure of the starting PK model will be based on the PK analysis

of data from previous studies. The CL/F and V/F of upadacitinib will be the PK parameters of major interest in the analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models.

1. The objective function of the best model is significantly smaller than the alternative model(s).
2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base PK model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using non-linear mixed effects modeling. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using stepwise forward selection method, or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary PK parameters with various covariates will be explored.

For the same subjects from whom the PK samples will be collected, relationships between upadacitinib exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored. The relationship between exposure (e.g., population PK model predicted average concentrations, area under the curve, trough concentrations, the individual model-predicted PK profiles, or some other appropriate measure of exposure) and drug effect will be explored. Several classes of models (e.g., linear, log-linear, exponential, E_{max}, sigmoid E_{max}, etc.) will be evaluated to characterize the exposure-response relationship based on observed data. Results of the pharmacokinetic and exposure-response analyses may be summarized in a separate report prior to regulatory filing of upadacitinib for the treatment of AD, rather than in the CSR.

Additional analyses will be performed if useful and appropriate.

7.6 Statistical Analysis of Immunophenotype Data and Optional Proteomic Biomarker Data

For biomarkers in T-lymphocyte, B-lymphocyte, and natural killer cells (TBNK) immunophenotype data (natural killer cells, natural killer T cells [NKT], B cells, and T cells) or optional whole blood proteomic and targeted serum protein investigations, summary statistics at Baseline and post treatment time points, in addition to change from Baseline at each time point will be provided; this will include mean, standard

deviation, median, quartiles, and range for each treatment group. The PD effect of each biomarker between the placebo and upadacitinib treatment groups will be evaluated via a mixed-effects modeling approach with change from Baseline of the biomarker score (after log transformation if appropriate) as response variable, Treatment, Time, and Treatment × Time interaction as fixed-effects, the corresponding Baseline biomarker score as a covariate, and "subjects nested within the treatment group" as a random-effect. Other Baseline covariates such as age, weight, etc., may be considered in the model if appropriate.

Additional analysis may be conducted on TBNK immunophenotype and/or optional proteomic biomarker data for the purpose of identification of prognostic, predictive, surrogate and PD biomarkers associated with efficacy or safety. The association of biomarkers to the efficacy or safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling approaches.

7.7 Interim Analysis

There will be no efficacy or futility interim analyses. Safety data will be reviewed by an external DMC as described in Section 6.3.

8 ETHICS

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

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

In Japan, the investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

In Japan, when important new information related to the subject's consent becomes available, the investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

8.2 Ethical Conduct of the Study

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

In the event of a state of emergency or pandemic (e.g., COVID-19) leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to the Operations Manual in Appendix F 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.

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

Electronic Patient Reported Data

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health; while the user acceptance testing of the study-specific patient reported outcome design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health. Daily Worst Pruritus NRS, daily and weekly ADerm-SS, and daily and weekly ADerm-IS ePROs will be collected from subjects electronically every evening via a handheld device provided to the subject at Screening. Handheld device usage stops at the Week 16 visit. The handheld electronic device will be programmed to allow data entry once per day. Starting at the Week 16 visit, Daily Worst Pruritus NRS, ADerm-SS, and ADerm-IS ePROs will be collected electronically via an onsite tablet device into which the subject will directly enter the required pieces of information at visits specified in the Operations Manual Section 2.1 (Appendix F) (Individual Treatment Period Visit Activities). The ePRO data of CDLQI, DLQI, HADS, POEM, PGIS, PGIT, PGIC, EQ-5D-5L, WPAI:AD, SF-36, and patient-reported items from SCORAD will be collected electronically via an onsite tablet device into which the subject will directly enter the required pieces of information at visits specified in the Operations Manual Section 2.1 (Appendix F) (Individual Treatment Period Visit Activities). The electronic tablet device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessments at any one visit. All data entered on the devices will be immediately stored to the devices itself and automatically uploaded to a central server administrated by CRF Health. The investigator and delegated staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

Photography

Photography data will be collected from subjects at select sites who consent to participate in the Photography sub-study and are considered eligible to be enrolled in this study. Subjects that consent to participate will be asked to have photographs taken of their disease response during the study. The photographs will be taken as outlined in Appendix D, Activity Schedule and in the Operations Manual Section 2.1 (Appendix F).

The cameras for the photographs will be standardized and supplied to the sites by a central photography service. The photography data on the server will be considered source; and maintained and managed by the vendor. Training and detailed instructions will be provided by the central photography service.

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.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AD	Atopic dermatitis
ADerm-IS	Atopic dermatitis impact scale
ADerm-SS	Atopic dermatitis symptom scale
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BSA	Body surface area
CAC	Cardiovascular Adjudication Committee
CD	Crohn's disease
CDLQI	Children's Dermatology Life Quality Index
CL/F	Oral clearance
CNS	Central nervous system
COVID-19	Coronavirus Disease – 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest x-ray
CYP3A	Cytochrome P450 3A
DB Period	double-blind treatment period
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
DTP	Direct-to-patient
EASI	Eczema Area and Severity Index
EASI 50/75/90	50%/75%/90% reduction in Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram

eCRF	Electronic case report form
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-anxiety
HADS-D	Hospital Anxiety and Depression Scale-depression
HB	hepatitis B
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HECSI	Hand eczema severity index
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C Reactive Protein
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IL	Interleukin
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional review board
ITT	Intent-to-Treat
ITT_A	Intent-to-Treat Population for adolescents
ITT_M	Intent-to-Treat Population for the main study
JAK	Janus kinase
MACE	Major adverse cardiac event
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
NKT	Natural killer T
NMSC	Non-melanoma skin cancer

NRI	Non-responder imputation
NRS	numerical rating scale
PD	Premature discontinuation
PDE4	Phosphodiesterase type 4
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGIT	Patient Global Impression of Treatment
PK	Pharmacokinetic
POEM	Patient oriented Eczema Measure
PPD	purified protein derivative
PPE	Personal Protective Equipment
PP_M	Per-Protocol Population for the main study
PRO	patient-reported outcome
PsA	Psoriatic arthritis
PT	Preferred term
QD	Once daily
QoL	Quality of Life
QTcF	Fridericia-corrected QT interval
RA	Rheumatoid arthritis
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SCORAD	Scoring atopic dermatitis
SCORAD 50/75/90	50%/75%/90% reduction in scoring atopic dermatitis
SF-36	Short Form Health Survey
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA SD	Therapeutic Area Scientific Director
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
Tdap	Tetanus-diphtheria-acellular pertussis
TEAE	Treatment-emergent adverse event
TNF	tumor necrosis factor

TPPA	Treponema pallidum particle agglutination assay
TRUST	Toluidine Red Unheated Serum Test
TSS-7	7-item total symptom score
TSS-11	11-item total symptom score
Tyk2	Tyrosine kinase 2
UC	Ulcerative colitis
ULN	Upper limit of normal
UV	Ultraviolet
VHP	Voluntary Harmonisation Procedure
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis
V/F	Volume of distribution
WBC	White blood cell
WPAI:AD	Work Productivity and Activity Impairment Index: Atopic Dermatitis

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-045: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 28 January 2021

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Pharmacology and Pharmacometrics
		Clinical Program Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Immunology Clinical Development
		Immunology Clinical Development
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across Screening and subsequent study visits. The individual activities are described in detail throughout the protocol and in the Operations Manual Section 2.1 (Appendix F). Allowed modifications due State of Emergency of Pandemic-Related Acceptable Protocol Modifications are detailed within Operations Manual.

Study Activities Table

Activity (timepoint clarifications in parentheses)	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 64 to Week 124 (Every 12 weeks) & Week 140	Phone Call (Week 152 and every 24 weeks until Week 248)	Site Visit (Week 164 and every 24 weeks until Week 260)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1																	
INTERVIEWS & QUESTIONNAIRES																			
Subject information and informed consent	✓																		
Eligibility criteria	✓	✓																	
Medical history	✓	✓																	
Drug and alcohol history	✓																		
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk factor questionnaire (annually after Week 52)	✓												✓	✓ (Week 100)		✓ (Weeks 164, 212, & 260)			
Review and document pregnancy avoidance recommendations (females of childbearing potential only) (every 12 weeks after the Week 124 visit)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Activity (timepoint clarifications in parentheses)	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 64 to Week 124 (Every 12 weeks) & Week 140	Phone Call (Week 152 and every 24 weeks until Week 248)	Site Visit (Week 164 and every 24 weeks until Week 260)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1																	
PRO																			
Worst Pruritus NRS, ADerm-SS, ADerm-IS (Hand-held device through Week 16. Week 16 and future visits should be on tablet)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓ (Worst pruritus NRS only)	✓	✓	
SCORAD (patient-reported items)		✓		✓				✓					✓				✓	✓	
CDLQI or DLQI, POEM (every 24 weeks after the Week 52 visit)		✓		✓		✓		✓		✓	✓	✓	✓	✓			✓	✓	
HADS (every 24 weeks after the Week 52 visit)		✓					✓	✓			✓		✓	✓				✓	
EQ-5D-5L (every 24 weeks after the Week 52 visit)		✓			✓			✓			✓		✓	✓				✓	
WPAI:AD (every 24 weeks after the Week 52 visit)		✓						✓				✓	✓	✓				✓	
SF-36(every 24 weeks after the Week 52 visit)		✓				✓		✓					✓	✓				✓	
PGIS, PGIC (except Baseline), PGIT		✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓				✓	
Subject hand-held device review (dispense at Screening)	✓	✓	✓	✓	✓	✓	✓	✓											

Activity (timepoint clarifications in parentheses)	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 64 to Week 124 (Every 12 weeks) & Week 140	Phone Call (Week 152 and every 24 weeks until Week 248)	Site Visit (Week 164 and every 24 weeks until Week 260)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1																	
EXAM																			
Body weight	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Height (adolescent subjects)	✓	✓				✓		✓		✓	✓	✓	✓	✓		✓		✓	
Height (adult subjects)		✓																	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Physical exam (every 24 weeks after Week 52)	✓	✓						✓					✓	✓		✓		✓	✓
Tanner staging (for adolescent subjects only, every 24 weeks after Week 52)		✓						✓		✓			✓	✓		✓		✓	
12-lead ECG (Baseline, annually, and PD)	✓												✓	✓ (Week 100)		✓ (Weeks 164, 212, & 260)		✓	
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator Assessments: EASI, BSA, vIGA, and HECSI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓ (excludes HECSI)	✓	✓	
Investigator Assessment: SCORAD		✓		✓				✓					✓				✓	✓	
Photography (select sites only)		✓		✓	✓			✓											

Activity (timepoint clarifications in parentheses)	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 64 to Week 124 (Every 12 weeks) & Week 140	Phone Call (Week 152 and every 24 weeks until Week 248)	Site Visit (Week 164 and every 24 weeks until Week 260)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1																	
Chest x-ray (annually starting Week 52 if newly positive TB test results, newly identified TB risk factors, or subject living in endemic areas)	✓												✓	✓ (Week 100)		✓ (Weeks 164, 212, & 260)			
Local LAB																			
Urine pregnancy test (for all female subjects of childbearing potential)		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Dispense urine pregnancy tests for monthly home testing										✓	✓	✓	✓	✓		✓			
Central LAB																			
Serum pregnancy test (for all female subjects of childbearing age)	✓																		

Activity (timepoint clarifications in parentheses)	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 64 to Week 124 (Every 12 weeks) & Week 140	Phone Call (Week 152 and every 24 weeks until Week 248)	Site Visit (Week 164 and every 24 weeks until Week 260)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1																	
hsCRP, clinical chemistry, hematology, urinalysis	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓ (excludes hsCRP)	✓	✓	✓ (only as needed for AEs)
TB Test (QuantiFERON TB Gold test [or interferon gamma release assay equivalent such as T-SPOT test] and/or local PPD skin test, if required) (annually after Week 52)	✓												✓	✓		✓			
HIV, HBV, and HCV	✓																		
Blood samples for Upadacitinib PK assay (PK samples will be collected from subjects at select sites)				✓		✓	✓	✓										✓ (through Week 16 only)	
Blood samples for TBNK immunophenotyping		✓				✓		✓											
Total IgE		✓						✓					✓						
Urine drug screen	✓																		
℞ TREATMENT																			
Randomization/Drug assignment		✓																	
Dispense Study Drug		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓			

ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptom Scale; AE = adverse event; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EQ-5D-5L = EuroQoL Dimensions 5 Levels; F/U = follow-up; HADS = Hospital Anxiety and Depression Scale; HBV = hepatitis B; HCV = hepatitis C; HECSI = Hand eczema severity index; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C reactive protein; IgE = immunoglobulin E; NRS = Numerical Rating Scale; PD = premature discontinuation; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PGIT = Patient Global Impression of Treatment; PK = pharmacokinetic; POEM = Patient-oriented Eczema Measure; PPD = purified protein derivative; SCORAD = Scoring atopic dermatitis; SF-36 = Short Form-36 Health Survey; TB = tuberculosis; TBNK = T lymphocyte, B-lymphocyte, and natural killer cells; vIGA = validated Investigator Global Assessment; Wk = week; WPAI:AD = Work Productivity and Activity Impairment Index: Atopic Dermatitis

Optional Biomarker Sample Activities Table

	Screening	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 64 to Week 124 (Every 12 weeks) & Week 140	Phone Call (Week 148 and every 24 weeks until Week 248)	Site Visit (Week 160 and every 24 weeks until Week 260)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
Activity		**D 1**																	
Whole blood for epigenetics (DNA) and Expression (RNA)		✓		✓	✓			✓											
Whole Blood for Proteomic and targeted protein investigations (serum)		✓		✓	✓			✓											
Whole Blood for Pharmacogenetic DNA (can also be drawn at any time during the study)		✓																	

D = day; DNA = deoxyribonucleic acid; F/U = follow-up; PD = premature discontinuation; RNA = ribonucleic acid; Wk = week

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	04 May 2018
Version 1.01 VHP	20 August 2018
Version 1.02 Canada	08 August 2018
Version 2.0	18 December 2018
Administrative Change 1	30 January 2019
Version 3.0	24 July 2019
Version 4.0	02 October 2019
Version 5.0	29 April 2020
Version 5.1 VHP	31 July 2020

The purpose of this Amendment is to incorporate the following changes:

Summary of Protocol Changes:

The primary purposes of this Amendment are to extend the blinded extension period from Week 136 to Week 260 and to incorporate necessary protocol modifications due to the COVID-19 pandemic. These changes and other clarifications are listed below.

The rationale for the following changes was to incorporate modifications due to the COVID-19 pandemic:

- Section 2.2 – Included information on the re-evaluation of the benefit and risk to subjects participating in the study. The benefit-risk profile of various immunomodulatory therapies is being evaluated.
- Section 5.5 – Added instructions referring to the Operations Manual for necessary changes to activities or procedures in the event of temporary study [drug] interruption/halt.
- Section 5.8 – Included information on DTP study drug shipment and details on time limits for study drug interruption.
- Section 5.9 – Clarified that protocol deviations may include modifications due to COVID-19.
- Section 5.10 – Updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic.
- Section 6.1 – Included information on how to handle COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events.

- Section 6.2 – Added instruction to interrupt study drug in subjects with confirmed diagnosis of COVID-19.
- Section 8.2 – Noted that AbbVie will modify the study protocol as necessary due to the pandemic, referring to the Operations Manual in Appendix F for additional details. Investigators must also notify AbbVie if any urgent safety measures are taken.
- Section 9 – Noted that remote monitoring may be employed as needed.
- Appendix D – Added reference to Operations Manual for allowed COVID-19 modifications.
- Appendix F – Operations Manual updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic.

Other protocol changes:

- Title page – Updated the Sponsor/Emergency Medical Contact for the study from [redacted] to [redacted]
- Section 1, Section 4.1, Section 5.7, Appendix D – Change the last date of the Blinded Extension Period from Week 136 to Week 260.

  Rationale: [redacted]
- Section 4.1, Section 7.1 – Added that an interim analysis after Week 140 may be performed after all subjects (main study and adolescent sub-study) have completed the study activities.

  Rationale: To provide longer term safety and efficacy data for the use of upadacitinib 15 mg or 30 mg in patients with moderate-to-severe atopic dermatitis.
- Section 5.3 – Provided guidance regarding the use of live vaccines.

  Rationale: Due to the study extension of 2 years**,** the longer period of the study increases the likelihood that a subject may require a live vaccine (e.g., adolescents who may need measles-mumps-rubella vaccine or varicella vaccine).
- Section 5.5, Section 6.2 – Provided definition of GI perforation.

  Rationale: To provide further clarity on the characterization of GI perforations for investigators.
- Section 6.2 – Updated Specific Toxicity Management Guidelines for Abnormal Laboratory Values for hemoglobin, absolute neutrophil count, ALT, and AST in Table 3.

  Rationale: Provided clarity regarding the management of abnormal hemoglobin, absolute neutrophil count, ALT/AST, and creatinine.
- Section 7.3 – Added for selected efficacy endpoints, long-term efficacy analysis will be performed using MI.

  Rationale: [redacted]

- Appendix D – Changed from Week 64 to Week 136 (every 12 weeks) to Week 64 to Week 124 (every 12 weeks) and Week 140.

  Rationale: To align the study visit and interval to accommodate the extension to Week 260.

- Appendix D – Added prior/concomitant therapy, review and document pregnancy avoidance recommendations, AE assessment at Week 152 to Week 260. Added latent TB risk factor questionnaire, body weight, height (adolescent subjects), vital signs, physical exam, Tanner staging, 12-lead ECG, chest x-ray, urine pregnancy test, dispense urine pregnancy test, clinical chemistry, hematology, urinalysis, TB test, and dispense study drug at Week 164 to Week 260.

  Rationale: Safety assessments will continue at all phone call and site visits to allow the monitoring of participant safety while receiving upadacitinib.

- Appendix D – Added Worst Pruritus NRS, EASI, BSA, and vIGA-AD at Week 164 to 260.

  Rationale: After Week 124, long-term efficacy measures conducted at the site will be simplified to measures of AD disease activity that study drug directly impacts.

- Appendix D, Appendix F – Specified that after Week 52, latent TB risk factor questionnaire, 12-lead ECG, and chest x-ray will be taken at Weeks 100, 164, 212, and 260.

- Appendix D – Clarified that blood samples for PK assay should not be taken at the PD Visit if the PD Visit occurs after Week 16.

- Appendix F – Updated the Operations Manual to reflect the extension of the Blinded Extension Period from Week 136 to Week 260.

- Appendix F – Updated the Sponsor/Emergency Medical Contact for the study from [redacted] to [redacted]

In addition to these modifications, this Amendment contains the following minor changes:

- Minor text edits as needed for consistency and clarity.
- Section 6.1, Appendix F – Updated contact number and email address for safety concerns.
- Appendix C – Updated list of protocol signatures.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M16-045 – Measure Up 1

Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Adolescent and Adult Subjects

SPONSOR:	For Non-EU Countries: AbbVie Inc. For EU Countries: AbbVie Deutschland GmbH & Co. KG (AbbVie)	ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib

FULL TITLE: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Mobile: [redacted] Email:
Safety Concerns	Therapeutic Area Safety Team 1 North Waukegan Road North Chicago, IL 60064	Toll Free: +1 (833) 942-2226 Email: SafetyManagement_TA@abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance@abbvie.com	Fax: 1 (847) 938-0660
Protocol Deviations	[redacted] AbbVie Inc. 41-45 Marinou Antypa Street 141 21 N. Irakleio Athens, Greece	Office: Fax: Email: [redacted]
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214	Phone: +1 (866) 762-6209 (Toll free) +1 (317) 271-1200 (Local calls) Fax: +1 (317) 616-2362 For country specific toll free numbers please refer to Covance Lab Manual.
Pharmacokinetic Lab	AbbVie Inc. Sample Receiving Dept. R46W, Bldg. AP13A, Rm. 2310 1 North Waukegan Rd. North Chicago, IL 60064	Phone: +1 (847) 937-0889 Fax: +1 (847) 938-9898
Exploratory Sample Lab	BioStorage Technologies Inc 2910 Fortune Circle West, Suite E Indianapolis, IN 46241	Phone: +1 (317) 268-5749 Fax: +1 (317) 390-1868

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to a state of emergency or pandemic (e.g., Coronavirus Disease – 2019 [COVID-19] pandemic). This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Visit window is ± 3 days until the Week 24 visit and beyond is a ± 7 day visit window. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Protocol Section 5.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

During a state of emergency or pandemic (e.g., COVID-19), if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the IRB/IEC and the subject, all visits with the exception of Week 16 may be conducted remotely or in the subject's home residence.
- Some study visits and/or activities may be performed by phone/virtually. These are indicated by a hashtag (#) in the appropriate visit tables below.
    - During a virtual visit, the Investigator assessments related to EASI, BSA, vIGA-AD, SCORAD, and HECSI will not be performed, as they need to be performed during an in-person assessment.
- Some study visits and/or activities may be performed by a local clinic/hospital/laboratory. These are indicated by a plus sign (+) in the appropriate visit tables below. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study Visits and/or activities should be performed as scheduled whenever possible.

- The Screening and Day 1 visits should be performed on site only.

If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity. Laboratory draws must be obtained within the protocol defined visit window for the scheduled visit.

Unscheduled phone/video visits should occur without lab testing; lab testing should be conducted at the earliest opportunity when the subject is able to be on-site.

SCREENING:

INTERVIEWS & QUESTIONNAIRES	• Subject Information and Informed consent for main study and for photography sub-study at select sites participating in the sub studies.	• Eligibility criteria • Medical history • Drug and Alcohol History • Prior/concomitant therapy • Latent Tuberculosis (TB) risk factor questionnaire
PRO	• Worst Pruritus Numerical Rating Scale (NRS) • Atopic Dermatitis Symptom Scale (ADerm-SS)	• Atopic Dermatitis Impact Scale (ADerm-IS) • Dispense subject hand-held device
EXAM	• Height (adolescent subjects only) • Body weight • Vital signs • Physical exam • 12-lead Electrocardiogram (ECG) • Adverse event (AE) assessment	• Investigator Assessments: Eczema Area and Severity Index (EASI), body surface area (BSA), validated Investigator Global Assessment (vIGA), and Hand Eczema Severity Index (HECSI) • Chest x-ray
CENTRAL LAB	• Serum pregnancy test (for all female subjects of childbearing potential) • High sensitivity C-reactive protein (hsCRP) • Clinical Chemistry • Hematology • Urinalysis • Urine drug screen	• TB Test (QuantiFERON TB Gold test [or interferon gamma release assay (IGRA) equivalent such as T-SPOT test] and/or local PPD skin test, if required) • Human immunodeficiency virus (HIV), Hepatitis B (HBV), and hepatitis C (HCV) Screening

Notes: The ECG obtained at Screening will serve as the Baseline reference.
All Screening procedures must be performed onsite.

BASELINE/DAY 1:

INTERVIEWS & QUESTIONNAIRES	• Eligibility criteria • Medical history • Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS • SCORing Atopic Dermatitis (SCORAD) (patient-reported items) • Children's Dermatology Life Quality Index (CDLQI) or Dermatology Life Quality Index (DLQI) • Patient-oriented Eczema Measure (POEM)	• Hospital Anxiety and Depress Scale (HADS) • EuroQoL Dimensions 5 Levels (EQ-5D-5L) • Work Productivity and Activity Impairment Index: Atopic Dermatitis (WPAI:AD) • Short Form-36 Health Survey (SF-36) • Patient Global Impression (PGI) of severity (PGIS)/ treatment (PGIT) • Subject hand-held device review
EXAM	• Height • Body weight • Vital signs • Physical exam • Tanner Staging (adolescent subjects only) • AE assessment	• Investigator Assessments (EASI, BSA, vIGA, SCORAD (patient-reported items), and HECSI) • Photography
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry • Hematology • Urinalysis • Blood samples for TBNK immunophenotyping • Total immunoglobulin E (IgE)	• Optional Biomarker: DNA/RNA • Optional Biomarker: Proteomic and targeted protein investigations (serum) • Optional Biomarker: whole blood for Pharmacogenetic DNA
TREATMENT	• Randomization/Drug assignment	• Dispense Study Drug

Notes: Baseline Visit procedures will serve as the reference for all subsequent visits.
Whole blood for Pharmacogenetic DNA is noted as being collected at Baseline, but it can be drawn at any time during the subject's participation in the study.

All Baseline/Day 1 procedures must be performed onsite.

WEEK 1:

INTERVIEWS & QUESTIONNAIRES	# Prior/concomitant therapy	# Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	# Worst Pruritus NRS # ADerm-SS # ADerm-IS	# PGIS, Patient Global Impression of Change (PGIC), PGIT # Subject hand-held device review
EXAM	# Vital signs # AE assessment	• Investigator Assessments (EASI, BSA, vIGA, and HECSI)

WEEK 2:

INTERVIEWS & QUESTIONNAIRES	# Prior/concomitant therapy	# Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	# Worst Pruritus NRS # ADerm-SS # ADerm-IS # SCORAD (patient-reported items)	# CDLQI or DLQI # POEM # PGIS, PGIC, PGIT # Subject hand-held device review
EXAM	# Vital signs # AE assessment • Photography	• Investigator Assessments (EASI, BSA, vIGA, SCORAD, and HECSI)
CENTRAL LAB	• hsCRP + Clinical Chemistry + Hematology + Urinalysis + Blood samples for upadacitinib pharmacokinetic (PK) assay (PK samples will be collected from subjects at select sites)	• Optional Biomarker: DNA/RNA • Optional Biomarker: Proteomic and targeted protein investigations (serum)

WEEK 4:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS,	#	EQ-5D-5L
	#	ADerm-SS,	#	PGIS, PGIC, PGIT
	#	ADerm-IS	#	Subject hand-held device review
EXAM	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Vital signs	•	Photography
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential		
CENTRAL LAB	+	hsCRP	•	Optional Biomarker: DNA/RNA
	+	Clinical Chemistry	•	Optional Biomarker: Proteomic and targeted protein investigations (serum)
	+	Hematology		
	+	Urinalysis		
TREATMENT	#	Dispense Study Drug		

WEEK 8:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	POEM
	#	ADerm-SS	#	SF-36
	#	ADerm-IS	#	Subject hand-held device review
	#	CDLQI or DLQI		
EXAM	#	Body Weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Height (adolescent subjects only)		
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential		
CENTRAL LAB	+	hsCRP	+	Blood samples for upadacitinib PK assay (PK samples will be collected from subjects at select sites)
	+	Clinical Chemistry	+	Blood samples for TBNK immunophenotyping
	+	Hematology		
	+	Urinalysis		
TREATMENT	#	Dispense Study Drug		

WEEK 12:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	PGIS, PGIC, PGIT
	#	ADerm-SS	#	Subject hand-held device review
	#	ADerm-IS		
	#	HADS		
EXAM	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential		
CENTRAL LAB	•	hsCRP	+	Blood samples for upadacitinib PK assay (PK samples will be collected from subjects at select sites)
	+	Clinical Chemistry		
	+	Hematology		
	+	Urinalysis		
TREATMENT	#	Dispense Study Drug		

WEEK 16:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS (completed on tablet during visit) • ADerm-SS (completed on tablet during visit) • ADerm-IS (completed on tablet during visit) • SCORAD (patient-reported items) • CDLQI or DLQI • POEM	• HADS • EQ-5D-5L • WPAI:AD • SF-36 • PGIS, PGIC, PGIT • Subject hand-held device review
EXAM	• Height (adolescent subjects only) • Body weight • Vital signs • Physical exam • AE assessment	• Tanner Staging (adolescent subjects only) • Investigator Assessments (EASI, BSA, vIGA, SCORAD, and HECSI) • Photography
LOCAL LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• hsCRP • Clinical Chemistry • Hematology • Urinalysis • Blood samples for upadacitinib PK assay (PK samples will be collected from subjects at select sites) • Blood samples for T-lymphocyte, B-lymphocyte, and natural killer cells (TBNK) immunophenotyping	• Total Immunoglobulin E (IgE) • Optional Biomarker: whole blood for DNA/RNA • Optional Biomarker: Proteomic and targeted protein investigations (serum)
TREATMENT	• Dispense Study Drug	

Note: This visit must be performed on site with all procedures completed including EASI prior to dispensation of Study Drug. If due to travel restrictions the subject cannot visit the site:

The upadacitinib/placebo kit can be sent via courier to the subject upon review of the available lab results as described above to continue treatment until the subject is able to visit the site for the Week 16 visit.

The Week 16 visit is critical for re-stratification and should be completed on-site as soon feasible, even if the timing falls into a future projected visit date. The Week 20 visit is important to occur four weeks after whenever the Week 16 visit occurs. If the delayed on-site Week 16 visit is at the time of the projected Week 20 date, then the Week 16 visit should be performed and the delayed Week 20 visit conducted four weeks later; and the Week 24 visit would be considered missed. The Week 32 visit should occur within the original visit window.

WEEK 20:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	ADerm-IS
	#	ADerm-SS		
EXAM	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential		
CENTRAL LAB	•	hsCRP	#	Hematology
	+	Clinical Chemistry	#	Urinalysis
TREATMENT	#	Dispense Study Drug		

WEEK 24:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	CDLQI or DLQI
	#	ADerm-SS	#	POEM
	#	ADerm-IS	#	PGIS, PGIC, PGIT
EXAM	#	Body weight	•	Tanner Staging (adolescent subjects only)
	#	Height (adolescent subjects only)	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential	#	Dispense Urine pregnancy tests for home testing
TREATMENT	#	Dispense Study Drug		

WEEK 32:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	POEM
	#	ADerm-SS	#	HADS
	#	ADerm-IS	#	EQ-5D-5L
	#	CDLQI or DLQI	#	PGIS, PGIC, PGIT
EXAM	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Height (adolescent subjects only)		
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential	#	Dispense Urine pregnancy tests for home testing
CENTRAL LAB	•	hsCRP	+	Hematology
	+	Clinical Chemistry	+	Urinalysis
TREATMENT	#	Dispense Study Drug		

WEEK 40:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	POEM
	#	ADerm-SS	#	WPAI:AD
	#	ADerm-IS	#	PGIS, PGIC, PGIT
	#	CDLQI or DLQI		
EXAM	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Height (adolescent subjects only)		
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential	#	Dispense Urine pregnancy tests for home testing
CENTRAL LAB	•	hsCRP	+	Hematology
	+	Clinical Chemistry	+	Urinalysis
TREATMENT	#	Dispense Study Drug		

WEEK 52:

INTERVIEWS & QUESTIONNAIRES	# Prior/concomitant therapy # Latent TB risk factor questionnaire	# Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	# Worst Pruritus NRS # ADerm-SS # ADerm-IS # SCORAD (patient-reported items) # CDLQI or DLQI # POEM	# HADS # EQ-5D-5L # WPAI:AD # SF-36 # PGIS, PGIC, PGIT
EXAM	# Height (adolescent subjects only) # Body weight # Vital signs • Physical exam # AE assessment	• Tanner Staging (adolescent subjects only) • Investigator Assessments (EASI, BSA, vIGA, SCORAD, and HECSI) • Chest x-ray • 12-lead ECG
LOCAL LAB	# Urine pregnancy test for all female subjects of childbearing potential	# Dispense Urine pregnancy tests for home testing
CENTRAL LAB	• hsCRP + Clinical Chemistry + Hematology + Urinalysis	+ TB Test (QuantiFERON TB Gold test [or IGRA equivalent such as T-SPOT test] and/or local PPD skin test, if required) + Total IgE
TREATMENT	# Dispense Study Drug	

Notes: 12-lead ECG can be completed at the next on-site visit if missed.
TB test and chest x-ray can be completed at the earliest opportunity if missed.

WEEK 64 to WEEK 124 (Every 12 Weeks) & Week 140:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
	#	Latent TB risk factor questionnaire (Week 100)		
PRO	#	Worst Pruritus NRS	#	HADS
	#	ADerm-SS	#	EQ-5D-5L
	#	ADerm-IS	#	WPAI:AD
	#	CDLQI or DLQI	#	SF-36
	#	POEM	#	PGIS, PGIC, PGIT
EXAM	#	Height (adolescent subjects only)	•	Tanner Staging (adolescent subjects only)
	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, and HECSI)
	#	Vital signs	•	Chest x-ray (Week 100)
	•	Physical exam	•	12-lead ECG (Week 100 only)
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential	#	Dispense Urine pregnancy tests for home testing
CENTRAL LAB	•	hsCRP	+	TB Test
	+	Clinical Chemistry		
	+	Hematology		
	+	Urinalysis		
TREATMENT	#	Dispense Study Drug		

Notes: Visits are every 12 weeks after the Week 52 visit up to Weeks 124 (Week 64, 76, 88, 100, 112, and 124).

CDLQI, DLQI, POEM, HADS, EQ-5D-5L, WPAI:AD, SF-36, Tanner Staging (adolescents only), and physical exam will be performed every 24 weeks after the Week 52 visit (Weeks 76, 100, and 124).

Chest x-ray should be performed at Week 52 and annually thereafter if newly positive TB results at Weeks 100, 164, 212, and 260.

Latent TB risk factor questionnaire and TB test (QuantiFERON TB Gold test [or IGRA equivalent such as T-SPOT test] and/or local PPD skin test, if required) should be performed annually after Week 52 and at Weeks 100, 164, 212, and 260.

Designated site personnel may administer PRO data collection over the phone. The date and time of PRO data collection should be recorded, and the primary site monitor will inform the site which PROs may be collected over the phone.

Phone Call (Week 152 and every 24 weeks until Week 248)				
INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential (every 12 weeks)
EXAM	#	AE assessment		

Notes: Visits are every 24 weeks after the Week 152 visit up to Week 248 (Weeks 176, 200, 224, and 248).

Site Visit (Week 164 and every 24 weeks until Week 260)				
INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential (every 12 weeks)
	#	Latent TB risk factor questionnaire (Weeks 164, 212, & 260)		
PRO	#	Worst Pruritus NRS		
EXAM	#	Body weight	#	AE assessment
	#	Height (adolescent subjects only)	•	Investigator Assessments (EASI, BSA, and vIGA)
	#	Vital signs	•	Chest x-ray (Weeks 164, 212, & 260)
	•	Physical exam		
	•	Tanner Staging (adolescent subjects only)		
	•	12-lead ECG (Weeks 164, 212, & 260)		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential	#	Dispense Urine pregnancy tests for home testing
CENTRAL LAB	+	Clinical Chemistry	+	TB Test
	+	Hematology		
	+	Urinalysis		
TREATMENT	+	Dispense Study Drug		

Notes: Visits are every 24 weeks after the Week 164 visit up to Week 260 (Weeks 188, 212, 236, and 260).
Designated site personnel may administer PRO data collection over the phone. The date and time of PRO data collection should be recorded, and the primary site monitor will inform the site which PROs may be collected over the phone.

Unscheduled Visit For Rescue Treatment:

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	CDLQI or DLQI
	#	ADerm-SS	#	SCORAD (if visit occurs prior to Week 52) (patient-reported items)
	#	ADerm-IS	#	POEM
EXAM	#	Body weight	•	Investigator Assessments (EASI, BSA, vIGA, SCORAD [if visit occurs prior to Week 52], and HECSI)
	#	Vital signs		
	#	AE assessment		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential		
CENTRAL LAB	•	hsCRP	+	Hematology
	+	Clinical Chemistry	+	Urinalysis

Note: After an unscheduled rescue visit, subjects will continue to follow the standard protocol visit schedule, as applicable from that date.

Designated site personnel may administer PRO data collection over the phone. The date and time of PRO data collection should be recorded, and the primary site monitor will inform the site which PROs may be collected over the phone.

PREMATURE D/C VISIT: ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ● ○

INTERVIEWS & QUESTIONNAIRES	#	Prior/concomitant therapy	#	Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	#	Worst Pruritus NRS	#	POEM
	#	ADerm-SS	#	HADS
	#	ADerm-IS	#	EQ-5D-5L
	#	SCORAD (if PD visit occurs prior to Week 52) (patient-reported items)	#	WPAI:AD
			#	SF-36
			#	PGIS, PGIC, PGIT
	#	CDLQI or DLQI		
EXAM	#	Height (adolescent subjects only)	•	Investigator Assessments (EASI, BSA, vIGA, SCORAD [if premature discontinuation (PD) visit occurs prior to Week 52], and HECSI)
	#	Body Weight		
	#	Vital signs		
	•	Physical exam		
	#	AE assessment		
	•	Tanner Staging (adolescent subjects only)		
	•	12-lead ECG		
LOCAL LAB	#	Urine pregnancy test for all female subjects of childbearing potential		
CENTRAL LAB	•	hsCRP	+	Blood samples for upadacitinib PK assay (PK samples will be collected from subjects at select sites)*
	+	Clinical Chemistry		
	+	Hematology		
	+	Urinalysis		

Note: Designated site personnel may administer PRO data collection over the phone. The date and time of PRO data collection should be recorded, and the primary site monitor will inform the site which PROs may be collected over the phone.

* Blood samples for PK assay should not be taken at the PD Visit if the PD Visit occurs after Week 16.

30-DAY F/U VISIT:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy
EXAM	# AE assessment # Body Weight # Vital signs • Physical exam
CENTRAL LAB	• hsCRP + Clinical Chemistry + Hematology + Urinalysis

Notes: This visit is 30 days after last dose of study drug.

For those subjects who prematurely discontinue the study, if the subject is willing, a 30-day follow-up visit may occur to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs. If a subject is discontinued from study drug, the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation.

Subjects who choose to discontinue study drug treatment, but continue to participate in the study, should complete a Premature Discontinuation Visit (PD Visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood sample collection for exploratory research and validation studies. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply.

Clinical laboratory collections should only be made if needed to continue monitoring of relevant AEs.

3 APPENDICES

3.1 STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AD	Atopic dermatitis
ADerm-IS	Atopic dermatitis impact scale
ADerm-SS	Atopic dermatitis symptom scale
AE	Adverse event
CDLQI	Children's Dermatology Life Quality Index
COVID-19	Coronavirus Disease – 2019
DLQI	Dermatology life quality index
EASI	Eczema Area and Severity Index
EQ-5D-5L	Euroqol Dimensions 5 Levels
HADS	Hospital Anxiety and Depression Scale
IGA	Investigator global assessment
NRS	Numerical rating scale
PD	Premature discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGIT	Patient Global Impression of Treatment
PK	Pharmacokinetic
POEM	Patient-oriented Eczema Measure
SAE(s)	Serious adverse event(s)
SCORAD	Scoring atopic dermatitis
SF-36	Short Form-36 Health Survey
TB	Tuberculosis
vIGA-AD	Validated Investigator Global Assessment for atopic dermatitis
WPAI:AD	Work Productivity and Activity Impairment Index: Atopic Dermatitis

3.2 PRURITUS (ITCH) NUMERICAL RATING SCALE (NRS) EXAMPLE

On a scale 0 to 10, with 0 being "no itch" and 10 being "worst imaginable itch," how would you rate your itch at its worst during the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10

No Itch Worst Imaginable Itch

Worst Pruritus NRS V1 © AbbVie 12-7-2017

3.3 ATOPIC DERMATITIS SYMPTOM SCALE (ADERM-SS) QUESTIONNAIRE EXAMPLE

Instructions: Please complete this part of the diary before you go to bed at night. The following questions are about your atopic dermatitis (AD), also known as eczema. For each question, please select the **box (☐)** under the number that best describes **your experience with AD** during the **past 24 hours**. There are no right or wrong answers.

1. During your **sleep hours**, how bad was your **worst itch** due to AD?	No itch										Worst imaginable itch
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. During your **awake** hours, how bad was your **worst itch** due to AD?	No itch										Worst imaginable itch
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. During the past 24 hours, how bad was your **worst skin pain** due to AD?	No pain										Worst imaginable pain
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Instructions: Please complete this part of the diary **once a week** before you go to bed at night. The following questions are about your atopic dermatitis (AD), also known as eczema. For each question, please select the **box (☐)** under the number that best describes **your experience with AD** during the **past 24 hours**. There are no right or wrong answers.

4. During the past 24 hours, how bad was your **worst skin cracking** due to AD?	No skin cracking … Worst imaginable skin cracking 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐
5. During the past 24 hours, how bad was your **worst pain caused by skin cracking** due to AD?	No pain … Worst imaginable pain 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐
6. During the past 24 hours, how bad was your **worst dry skin** due to AD?	No dry skin … Worst imaginable dry skin 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐
7. During the past 24 hours, how bad was your **worst skin flaking** due to AD?	No flaking … Worst imaginable flaking 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐
8. During the past 24 hours, how bad was your **worst rash (redness, blisters, bumpy skin)** due to AD?	No rash … Worst imaginable rash 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐
9. During the past 24 hours, how bad was your **worst skin thickening** due to AD?	No skin thickening … Worst imaginable skin thickening 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

10. During the past 24 hours, how bad was your **worst bleeding** due to AD?	No bleeding										Worst imaginable bleeding
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11. During the past 24 hours, how bad was your **worst skin oozing** due to AD?	No oozing										Worst imaginable oozing
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

AD Symptoms Scale (ADerm-SS)-English-USA-V2

3.4 ATOPIC DERMATITIS IMPACT SCALE (ADERM-IS) QUESTIONNAIRE EXAMPLE

Instructions: The following questions are about your AD, also known as eczema. For each question, please select the **box (☐)** below the number that best describes your **experience with AD** during the **past 24 hours**. There are no right or wrong answers.

1. During your **sleep hours**, how **difficult** was it for you to **fall asleep** due to AD?	Not difficult — Extremely difficult 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
2. During your **sleep hours**, how **much** did your AD **impact your sleep**?	Not at all — Extremely 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
3. During your **sleep hours**, how **bothersome** was **waking up at night** due to AD?	Not bothersome — Extremely bothersome 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Instructions: The following questions are about your AD, also known as eczema. For each question, please select the **box (☐)** below the number that best describes your **experience with AD** during the **past seven days**. There are no right or wrong answers.

4. During the past seven days, how much did your AD **limit** your **household activities** (e.g., washing dishes, sweeping, doing laundry)?	Not limited — Extremely limited 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
5. During the past seven days, how much did your AD **limit** your **physical activities** (e.g., walking, exercising)?	Not limited — Extremely limited 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

6. During the past seven days, how much did your AD **limit** your **social activities**?	Not limited										Extremely limited
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. During the past seven days, how **difficult** was it for you **to concentrate** due to AD?	Not difficult										Extremely difficult
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. During the past seven days, how **self-conscious** did you feel due to AD?	Not self-conscious										Extremely self-conscious
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. During the past seven days, how **embarrassed** did you feel due to AD?	Not embarrassed										Extremely embarrassed
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10. During the past seven days, how **sad** did you feel due to AD?	Not sad										Extremely sad
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

AD Impact Scale (ADerm-IS)-English-USA-V2

3.5 DERMATOLOGY LIFE QUALITY (DLQI) EXAMPLE

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	 Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check you have answered EVERY question. Thank you.

3.6 CHILDREN'S DERMATOLOGY LIFE QUALITY (CDLQI) EXAMPLE

Hospital No
Name: Diagnosis: CDLQI SCORE: ☐
Age:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** ⇒ **If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR		
	was it **holiday time?** ⇒ **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

3.7 PATIENT ORIENTED ECZEMA MEASURE (POEM) EXAMPLE

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

Patient Details: _____

_____

_____

_____ Date: _____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

Total POEM Score (Maximum 28): .....

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	= 0
1-2 days	= 1
3-4 days	= 2
5-6 days	= 3
Every day	= 4

Note:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are selected, the response option with the highest score should be recorded

What does a poem score mean?

To help patients and clinicians to understand their POEM scores, the following bandings have been established (see references below):

• 0 to 2	= Clear or almost clear
• 3 to 7	= Mild eczema
• 8 to 16	= Moderate eczema
• 17 to 24	= Severe eczema
• 25 to 28	= Very severe eczema

Do I need permission to use the scale?

Whilst the POEM scale is protected by copyright, it is freely available for use and can be downloaded from: www.nottingham.ac.uk/dermatology
We do however ask that you register your use of the POEM by e-mailing cebd@nottingham.ac.uk with details of how you would like to use the scale, and which countries the scale will be used in.

References

Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. Arch Dermatol. 2004;140:1513-1519

Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol. Dec 2013; 169(6): 1326–1332.

3.8 HOSPITAL ANXIETY AND DEPRESS SCALE (HADS)

Hospital Anxiety and Depression Scale (HADS)

GL assessment

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		
		I feel tense or 'wound up'	
3		Most of the time	
2		A lot of the time	
1		From time to time, occasionally	
0		Not at all	
		I still enjoy the things I used to enjoy	
	0	Definitely as much	
	1	Not quite so much	
	2	Only a little	
	3	Hardly at all	
		I get a sort of frightened feeling as if something awful is about to happen	
3		Very definitely and quite badly	
2		Yes, but not too badly	
1		A little, but it doesn't worry me	
0		Not at all	
		I can laugh and see the funny side of things	
	0	As much as I always could	
	1	Not quite so much now	
	2	Definitely not so much now	
	3	Not at all	
		Worrying thoughts go through my mind	
3		A great deal of the time	
2		A lot of the time	
1		Not too often	
0		Very little	
		I feel cheerful	
	3	Never	
	2	Not often	
	1	Sometimes	
	0	Most of the time	
		I can sit at ease and feel relaxed	
0		Definitely	
1		Usually	
2		Not often	
3		Not at all	

A	D		
		I feel as if I am slowed down	
	3	Nearly all the time	
	2	Very often	
	1	Sometimes	
	0	Not at all	
		I get a sort of frightened feeling like 'butterflies' in the stomach	
0		Not at all	
1		Occasionally	
2		Quite often	
3		Very often	
		I have lost interest in my appearance	
	3	Definitely	
	2	I don't take as much care as I should	
	1	I may not take quite as much care	
	0	I take just as much care as ever	
		I feel restless as if I have to be on the move	
3		Very much indeed	
2		Quite a lot	
1		Not very much	
0		Not at all	
		I look forward with enjoyment to things	
	0	As much as I ever did	
	1	Rather less than I used to	
	2	Definitely less than I used to	
	3	Hardly at all	
		I get sudden feelings of panic	
3		Very often indeed	
2		Quite often	
1		Not very often	
0		Not at all	
		I can enjoy a good book or radio or television programme	
	0	Often	
	1	Sometimes	
	2	Not often	
	3	Very seldom	

Now check that you have answered all the questions

		A	D
	TOTAL		

3.9 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: ATOPIC DERMATITIS V2.0 (WPAI:AD)

The following questions ask about the effect of your AD on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____NO ___YES
   If NO, check "NO" and skip to question 6

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your AD? *Include hours you missed on sick days, times you went in late, left early, etc. because of AD. Do not include time you missed to participate in this study.*
   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
   _____HOURS

4. During the past seven days, how many hours did you actually work?
   _____HOURS *(If "0," skip to question 6)*

5. During the past seven days, how much did AD affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If AD affected your work only a little, choose a low number. Choose a high number if AD affected your work a great deal.

Consider only how much AD affected productivity while you were working.

Atopic dermatitis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Atopic dermatitis completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did AD affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If AD affected your

activities only a little, choose a low number. Choose a high number if AD affected your activities a great deal.

Consider only how much AD affected your ability
to do your regular daily activities, other than work at a job.

Atopic dermatitis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Atopic dermatitis completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:AD v2.0 (US English)

3.10 EUROQOL DIMENSIONS 5 LEVELS (EQ-5D-5L) QUESTIONNAIRE

EQ-5D-5L Tablet version	
English (USA)	Country (Language)
Health Questionnaire	Health Questionnaire
English version for the USA	Version (Target Language)
	Version (English)
Please tap the ONE box that best describes your health TODAY.	Instruction
MOBILITY	**Mobility**
I have no problems walking	MB1
I have slight problems walking	MB2
I have moderate problems walking	MB3
I have severe problems walking	MB4
I am unable to walk	MB5
SELF-CARE	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
PAIN / DISCOMFORT	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5

ANXIETY / DEPRESSION	Anxiety / Depression
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
This scale is numbered from 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health
Next	button.next
Previous	button.previous
© EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation	
Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*	

3.11 PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) QUESTIONNAIRE EXAMPLE

Seven point response scale

Please mark an "X" in the box (☒) that best describes the severity of your AD symptoms right now.

1. Right now, my AD symptoms are:

☐0 **Absent:** No symptoms

☐1 **Minimal:** Can be easily ignored without effort

☐2 **Mild:** Can be ignored with effort

☐3 **Moderate:** Cannot be ignored but does not influence my daily activities

☐4 **Moderately severe:** Cannot be ignored and occasionally limits my daily activities

☐5 **Severe:** Cannot be ignored and often limits my concentration on daily activities

☐6 **Very severe:** Cannot be ignored and markedly limits my daily activities.

3.12 PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) QUESTIONNAIRE EXAMPLE

Seven-point response scale

Please mark an "X" in the box (☒) that best describes the severity of your AD symptoms right now.

1. Compared to before your study treatment began, how would you rate the overall change in your AD symptoms?:

☐1 **Very much improved**

☐2 **Much improved**

☐3 **Minimally improved**

☐4 **No change**

☐5 **Minimally worse**

☐6 **Much worse**

☐7 **Very much worse**

3.13 PATIENT GLOBAL IMPRESSION OF TREATMENT (PGIT) QUESTIONNAIRE EXAMPLE

Seven-point response scale

Please mark an "X" in the box (☒) that best describes how satisfied or dissatisfied you are overall with your current treatment for AD.

1. Overall, how satisfied or dissatisfied are you with your current treatment for AD?:

☐1 **Extremely dissatisfied**

☐2 **Very dissatisfied**

☐3 **Somewhat dissatisfied**

☐4 **Neither dissatisfied nor satisfied**

☐5 **Somewhat satisfied**

☐6 **Very satisfied**

☐7 **Extremely satisfied**

3.14 SHORT FORM-36 (SF-36) HEALTH SURVEY

SF-36v2® Health Survey © 1992, 1996, 2000, 2010 Medical Outcomes Trust and QualityMetric Incorporated. All Rights Reserved. SF-36® is a registered trademark of Medical Outcomes Trust. (SF-36v2® Health Survey Standard, United States (English))
Your Health and Well-Being This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one response that best describes your answer.
In general, would you say your health is: Excellent Very good Good Fair Poor
Compared to one year ago, how would you rate your health in general now? Much better now than one year ago Somewhat better now than one year ago About the same as one year ago Somewhat worse now than one year ago Much worse now than one year ago

The following question is about activities you might do during a typical day. Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in lifting or carrying groceries? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in climbing several flights of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in climbing one flight of stairs? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

The following question is about activities you might do during a typical day. Does your health now limit you in bending, kneeling, or stooping? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking more than a mile? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking several hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in walking one hundred yards? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all
The following question is about activities you might do during a typical day. Does your health now limit you in bathing or dressing yourself? If so, how much? Yes, limited a lot Yes, limited a little No, not limited at all

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the amount of time you spent on work or other activities as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Were limited in the kind of work or other activities as a result of your physical health All of the time Most of the time Some of the time A little of the time None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities? Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious) All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Not at all Slightly Moderately Quite a bit Extremely
How much bodily pain have you had during the past 4 weeks? None Very mild Mild Moderate Severe Very Severe
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? Not at all A little bit Moderately Quite a bit Extremely

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks did you feel full of life?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you been very nervous?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks have you felt calm and peaceful?

All of the time
Most of the time
Some of the time
A little of the time
None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you have a lot of energy? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you felt downhearted and depressed? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you feel worn out? All of the time Most of the time Some of the time A little of the time None of the time
This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks have you been happy? All of the time Most of the time Some of the time A little of the time None of the time

This question is about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks did you feel tired? All of the time Most of the time Some of the time A little of the time None of the time
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? All of the time Most of the time Some of the time A little of the time None of the time
How TRUE or FALSE is the following statement for you? I seem to get sick a little easier than other people. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? I am as healthy as anybody I know. Definitely true Mostly true Don't know Mostly false Definitely false

How TRUE or FALSE is the following statement for you? I expect my health to get worse. Definitely true Mostly true Don't know Mostly false Definitely false
How TRUE or FALSE is the following statement for you? My health is excellent. Definitely true Mostly true Don't know Mostly false Definitely false

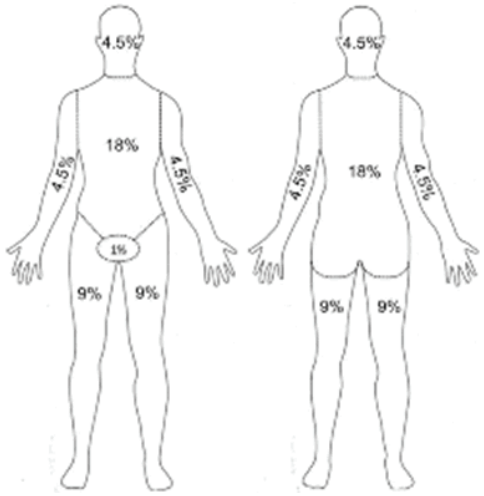
3.15 SCORING ATOPIC DERMATITIS (SCORAD) EXAMPLE

M16-045: SCORing Atopic Dermatitis (SCORAD) Worksheet

Subject Number: _____

Visit Date: _____ (DD-MMM-YYYY)

A. Body Area Affected: The score for each area is added up. The total area is 'A,' which has a possible maximum of 100%.



Body Area	Percentage (%) Affected (Use rule of 9's for each body area)
Head and neck (0% - 9%)	
Upper Limbs (0% - 18%)	
Trunk (0% - 36%)	
Genitals (0% - 1%)	
Lower Limbs (0% - 36%)	
A. Total	Total area will be calculated by the eCRF automatically.

B. Intensity of Symptoms: A representative area of eczema is selected. In this area, the intensity of each of the 6 specific symptoms is assessed as: none (0), mild (1), moderate (2) or severe (3).

Criteria	Intensity (0-3)
Erythema	
Edema/Papulation	
Scabs/Oozing	
Excoriation	
Lichenification	
Skin Dryness*	
B. Total	Total will be calculated by the eCRF automatically.

*Skin Dryness is assessed in an area where there is no inflammation.

C. Subjective Symptoms

See Study M16-045 electronic tablet for scoring of subjective symptoms.

The SCORAD is calculated as: [A/5 + 7B/2 + C].

Assessor (Print Name)	Signature	Date (dd-mmm-yyyy)

3.16 VALIDATED INVESTIGATOR'S GLOBAL ASSESSMENT FOR ATOPIC DERMATITIS (vIGA-AD) EXAMPLE

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 - Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 - Almost Clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 - Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 - Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 - Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 - Moderate."*

2. Excoriations should not be considered when assessing disease severity.

3.17 ECZEMA AREA AND SEVERITY INDEX (EASI) SCORING EXAMPLE

An EASI score is a tool used to measure the extent (area) and severity of atopic eczema (Eczema Area and Severity Index). EASI score does not include a grade for dryness or scaling.

Assignments for the following body regions are as follows:

- Head and Neck
- Trunk: (including the genital area)
- Upper extremities
- Lower extremities (including the buttocks)

Area Score

Area score is recorded for each of the four regions of the body. The area score is the percentage of skin affected by eczema.

Area score Percentage of skin affected by eczema in each region:

- 0 = no eczema in this region
- 1 = 1% – 9%
- 2 = 10% – 29%
- 3 = 30% – 49%
- 4 = 50% – 69%
- 5 = 70% – 89%
- 6 = 90% – 100%: the entire region is affected by eczema

Severity Score

Severity score is recorded for each of the four regions of the body. The severity score is the sum of the intensity scores for four signs.

The four signs are:

1. Redness (erythema, inflammation)
2. Thickness (induration, papulation, swelling – acute eczema)
3. Scratching (excoriation)

4. Lichenification (lined skin, prurigo nodules – chronic eczema)

The average intensity of each sign in each body region is assessed as: none (0), mild (1), moderate (2) and severe (3).

Score Intensity of redness, thickness/swelling, scratching, lichenification:

0 = None, absent

1 = Mild

2 = Moderate

3 = Severe

For each region, record the intensity for each of four signs and calculate the severity score.

Severity score = redness intensity + thickness intensity + scratching intensity + lichenification intensity

For each region, multiply the severity score by the area score and by a multiplier.

- Head and neck: severity score × area score × 0.1
- Trunk: severity score × area score × 0.3
- Upper limbs: severity score × area score × 0.2
- Lower limbs: severity score × area score × 0.4

Add up the total scores for each region to determine the final EASI score. The minimum EASI score is 0 and the maximum EASI score is 72.

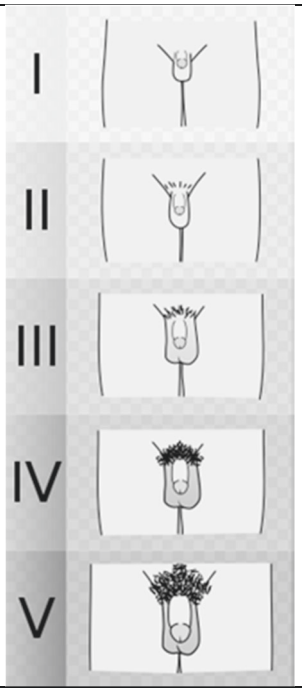
3.18 TB RISK ASSESSMENT FORM EXAMPLE

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
   - Africa
   - Eastern Europe
   - Asia
   - Latin America
   - Caribbean Islands
   - Russia
3. Have you lived or worked in a prison, homeless shelter/refugee camp, immigration center, health care worker in a hospital or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
   - Chronic Cough
   - Chest pain, or pain with breathing or coughing
   - Blood-Streaked Sputum (coughing up blood)
   - Unexplained Weight Loss
   - Fever
   - Fatigue/Tiredness
   - Night Sweats
   - Shortness of Breath

From: http://www.mayoclinic.org/diseases-conditions/tuberculosis/symptoms-causes/dxc-20188557
http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

3.19 TANNER STAGING EXAMPLE

BOYS

Stage	Pubic Hair		
□ 1	None		
□ 2	Scanty, long, slightly pigmented		
□ 3	Darker, starts to curl, small amount		
□ 4	Resembles adult type, less in quantity; coarse, curly		
□ 5	Adult distribution, spread to medial surface of thighs		
	Genitals		
Stage	**Penis**	**Testes**	
□ 1	Preadolescent	Preadolescent	
□ 2	Slight enlargement	Enlarged scrotum, pink texture altered	
□ 3	Longer	Larger	
□ 4	Larger, glans and breadth increase in size	Larger, scrotum dark	
□ 5	Adult	Adult	

GIRLS

Stage	Breasts
□ 1	Preadolescent
□ 2	Breast and papilla elevated as small mound, aureolar diameter increased
□ 3	Breast and areola enlarged. No contour separation
□ 4	Areola and papilla form secondary mound
□ 5	Mature, nipple projects, areola part of general breast contour
Stage	**Pubic Hair**
□ 1	None
□ 2	Sparse, lightly pigmented, straight, medial border of labia
□ 3	Darker, beginning to curl, increased amount
□ 4	Coarse, curly, abundant but amount less than in adult
□ 5	Adult feminine triangle, spread to medial surface of thighs