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Protocol for Study M16-047 – AD Up

Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Combination with Topical Corticosteroids 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 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. Upadacitinib (ABT-494) is a novel selective JAK1 inhibitor being developed for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, 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 and Endpoints:	To assess the efficacy and safety of upadacitinib combined with topical corticosteroids 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.
Investigators:	Multi-center; investigator information on file at AbbVie.
Study Sites:	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:
	  • EASI score ≥ 16 at the Screening and Baseline Visits;
	  • vIGA-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 inhibitor (TCI) OR documented systemic treatment for AD within 6 months prior to the Baseline Visit.
	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 ≥ 30% of AD lesional surface involvement at Baseline that cannot be safely treated with medium or higher potency TCS (e.g., areas of skin atrophy, face, groin, intertriginous areas).
	• 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 at Baseline 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 for up to Week 136.
Date of Protocol Synopsis:	29 April 2020

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, psoriatic arthritis, ulcerative colitis, 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 this 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 adverse event (AE), 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 already available as peer-reviewed manuscripts.[2-5] Results from a Phase 2 study in AD showed the upadacitinib doses of 15 mg to 30 mg per day had efficacy and safety profiles that can benefit patients with moderate to severe AD.

Clinical Hypothesis

Upadacitinib combined with topical corticosteroids (TCS) is expected to provide better efficacy compared with placebo combined with TCS and to 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] In addition, nearly 50% of dupilumab subjects who were IGA 0 or 1 responders at Week 16 became nonresponders 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 T helper 2 cell-mediated skin inflammation and itch mediated by JAK1 signaling in AD, 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 results demonstrate 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.

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

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

To assess the efficacy and safety of upadacitinib combined with TCS 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 a 90% reduction in EASI (EASI 90) at Week 16;
- Percent change from Baseline of Worst Pruritus NRS at Week 16;
- Percent change in EASI score from Baseline 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 4;
- Proportion of subjects achieving EASI 75 at Week 2;
- Proportion of subjects achieving EASI 90 at Week 4;
- Proportion of subjects achieving EASI 100 at Week 16 for 30 mg;
- 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.

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 4;
- Proportion of subjects achieving EASI 75 at Week 2;
- Proportion of subjects achieving EASI 90 at Week 4;
- Proportion of subjects achieving EASI 100 at Week 16 for 30 mg;
- 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.

3.4 Additional Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all visits other than 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;
- Proportion of subjects achieving EASI 50 at Week 2;
- 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;
- Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16;
- Proportion of subjects achieving EASI 50;
- Number of TCS free days with EASI 75 response up to Week 16*;
- Number of medium or higher potency TCS free days with EASI 75 response up to Week 16*;
- Time to first discontinuation of all TCS with EASI 75 response (discontinuation of all TCS is defined as the subject stops the TCS treatment > 7 consecutive days) up to Week 16*;
- Proportion of subjects achieving Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline;
- Change from Baseline in Worst Pruritus NRS;
- Percent change from Baseline in Scoring AD (SCORAD);

- Proportion of subjects achieving 50%/75%/90% reduction in SCORAD (SCORAD 50/75/90) from Baseline;
- Change from Baseline in body surface area (BSA);
- 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);
- 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, 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 and percent change from Baseline in Hospital Anxiety and Depression Scale (HADS) (total score, HADS-anxiety [HADS-A], HADS-depression [HADS-D]);
- Proportion of subjects achieving HADS-A < 8 and HADS-D < 8 for subjects with HADS-A ≥ 8 or HADS-D ≥ 8 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) 7-item total symptom score (TSS-7) ≥ 28 (minimal clinically important difference [MCID]) from Baseline 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-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 to items 1 – 11 of the ADerm-SS;
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥ 4 (MCID) from Baseline for subjects with ADerm-SS skin pain score ≥ 4 at Baseline;
- 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-SS TSS-7, ADerm-SS TSS-11, and skin pain score;
- Proportion of subjects achieving an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) sleep domain score ≥ 12 (MCID) from Baseline for subjects with ADerm-IS sleep domain score ≥ 12 at Baseline;
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS emotional state domain score ≥ 11 (MCID) from Baseline 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 for subjects with ADerm-IS daily activities domain score ≥ 14 at Baseline;
- Change and percent change from Baseline in ADerm-IS sleep domain score, emotional state domain score, and daily activities domain score;
- Proportion of subjects achieving an improvement (reduction) of Patient-oriented Eczema Measure (POEM) ≥ 4 from Baseline for subjects with POEM ≥ 4 at Baseline;
- 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 POEM;
- Proportion of subjects age ≥ 16 years old at screening achieving an improvement (reduction) of Dermatology Life Quality Index (DLQI) ≥ 4 for subjects with DLQI ≥ 4 at Baseline;
- Proportion of subjects age ≥ 16 years old at screening achieving DLQI score of 0/1 for subjects with DLQI score > 1 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 0/1 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: AD (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 Dermatologic Intimacy Scale (DIS) among adults;
- 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 vIGA-AD of 0 with a reduction from Baseline of ≥ 2 points.

*Note: Days from the start of systemic rescue will not be considered as TCS-free days.

3.5 Safety Endpoints

The following safety evaluations will be performed during the study: treatment emergent adverse events (TEAEs), SAEs, AEs of special interest (AESIs), AEs leading to discontinuation, vital signs, and laboratory tests.

3.6 Pharmacokinetic Endpoint

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, TNF), or other genes believed to be related AD, and other inflammatory diseases (filaggrin, Claudin-1, human leukocyte antigen). 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 multicenter study that will evaluate upadacitinib combined with TCS in adolescents (12 to 17 years of age) and adults (18 to 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.

The study is comprised of a 35-day screening period, a 16 week DB Period, a Blinded Extension Period of up to Week 136, 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 concomitant TCS with either daily oral doses of upadacitinib 15 mg (N = 270) or 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] versus 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] versus severe [vIGA-AD 4]) and by geographic region (US/Puerto Rico/Canada and Other). See Section 5 for information regarding eligibility criteria.

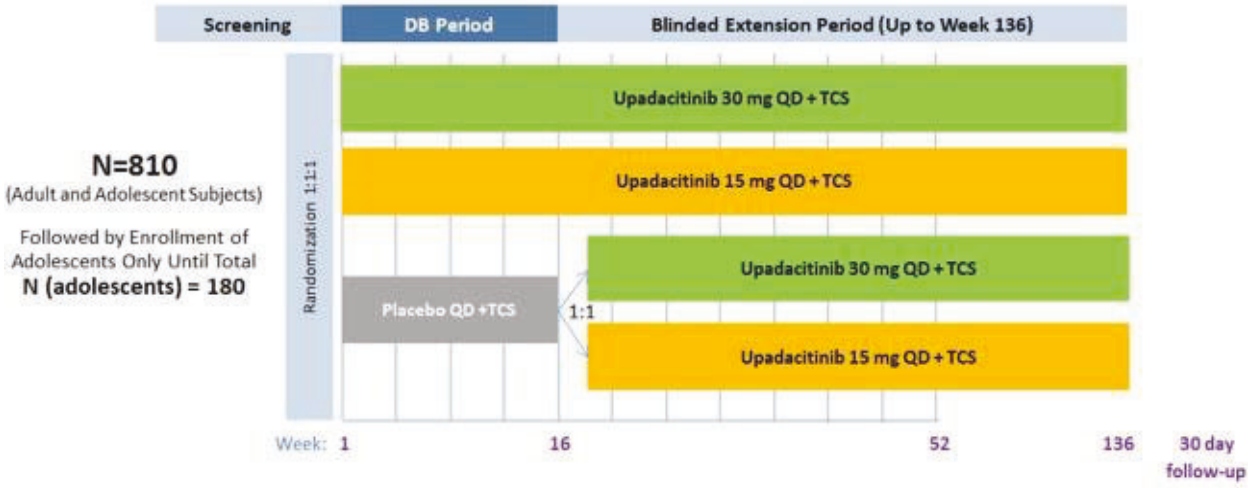
At the end of the 16 week DB period, subjects in the placebo group will be re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg during the Blinded Extension Period. Subjects originally in the 15 mg QD and 30 mg QD upadacitinib group will continue their treatment into the Blinded Extension Period up to the Week 136 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, 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. An additional analysis of the adolescent population will be conducted after all ongoing adolescent subjects have provided at least 1 year of upadacitinib exposure. 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; TCS = topical corticosteroids

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

TCS inhibitors permitted for use in areas where TCS is generally not advisable.

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, especially for long-term use. There is no anticipated medical risk for subjects randomized to placebo and background concomitant TCS; if needed, rescue treatment will be available for these subjects.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with AD. 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.[17-21]

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 2b 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 daily regimen 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). The literature suggests that maturation of the CYP3A activity in children 2 years and above is similar to that of adults.[22] 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 AD.

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 treatment period is deemed to be a sufficient duration to be able to test the superiority of upadacitinib in combination with TCS versus placebo in combination with TCS 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 age ≥ 12 to < 18 years old may 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 or their legally authorized representative 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 subject 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, 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.[23]
- 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 prior to the Baseline Visit) of inadequate response to TCS or topical calcineurin inhibitor (TCI) OR documented systemic treatment for AD within 6 months prior to the Baseline Visit.

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 ≥ 30% of AD lesional surface involvement at Baseline that cannot be safely treated with medium or higher potency TCS (e.g., areas of skin atrophy, face, groin, intertriginous areas).
- 17. 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;
  - 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, TCI, or topical PDE4 inhibitors within 7 days.
- 18. 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.
- 19. No systemic use of known strong CYP3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to Table 1 for examples of commonly used strong CYP3A inhibitors and inducers).
- 20. 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

- 21. 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 (WBC) count < 2,500/µL;
- Absolute neutrophil count (ANC) < 1,500/µL;
- Platelet count < 100,000/µL;
- Absolute lymphocyte count < 800/µL;
- Hemoglobin < 10 g/dL.

22. 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 positive or detected sensitivity on the HBV deoxyribonucleic acid polymerase chain reaction qualitative test for hepatitis B core antibody positive subjects (and for hepatitis B surface antibody positive where mandated per local requirements);
  - HCV: HCV ribonucleic acid detectable in any subject with anti-HCV antibody.
- In Japan, positive result of beta-D-glucan or two consecutive indeterminate results of beta-D-glucan (screening for pneumocystis jiroveci infection at central lab).

23. Subjects 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, the investigator determines 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 the investigator determines, 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

- 24. 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.
- 25. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.
- 26. No contraindication to topical corticosteroids or topical calcineurin inhibitors.

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.
- 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.

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.

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.

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, tofacitinib, baricitinib, abrocitinib [PF-04965842], and filgotinib) are 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 therapy for the treatment of AD is prohibited while on 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 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 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 allowed corticosteroid rescue.

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 psoralen and UVA 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

Aside from the required topical treatments (see Required Concomitant Medications in Section 5.4), no other topical treatments for AD should be started through Week 52 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 Inclusion Criterion 8.

Starting at the Week 52 Visit, the use of any concomitant topical medication for AD 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 Medical Director (TA MD).

Vaccines

Live vaccines are not permitted during study participation and including up to 4 weeks (or longer if required locally) after the last dose of study drug. 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; 8 weeks for subjects in Japan), before first dose of study drug with appropriate precautions. Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. Examples of live vaccines include, but are not limited to, the following:

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

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 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 TA MD should be contacted.

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 52. Starting at the Week 52 Visit, the use of emollients can be administered per investigator decision.

Note: Until Week 52, 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.

Starting at the Baseline Visit and continuing through Week 52, all subjects will initiate treatment with TCS and/or TCI with the following step-down regimen:

- Apply medium potency TCS QD to areas with active lesions for a maximum of 3 consecutive weeks. Low potency TCS or TCI should be applied QD on areas of thin skin (face, neck, intertriginous and genital areas) or for areas where medium TCS are considered unsafe (e.g., areas of skin atrophy). See Table 2 for types and potency levels of recommended TCS.

- After lesions are under control (clear or almost clear) or after 3 consecutive weeks of medium potency TCS QD, switch from medium potency to low potency TCS and treat QD for 7 days, then stop. For sensitive skin locations, low-potency TCS, or TCI are to be tapered and stopped.
- If lesions return or persist, resume treatment with the step-down approach described above until lesion resolution as long as there is no sign of local or systemic TCS toxicity.
- The subject should be monitored for signs of local or systemic TCS toxicity and step down or stopping treatment should be performed as necessary. Topical therapy may be further limited in duration and potency if medically advisable (e.g., in subjects with extensive TCS pretreatment and clinical signs of TCS side effects such as striae, skin atrophy, or bruising).
- At or after Week 4, see also Rescue Therapy below for further details on rescue treatment options with higher potency TCS or systemic therapy.
- At or after Week 52, the use of any concomitant topical medication for AD can be administered per investigator discretion and is no longer required.

Table 2. Potency Levels of Recommended Topical Corticosteroids*

Potency†	Recommended Topical Steroids
Low‡	Hydrocortisone 1% cream
Medium	Triamcinolone acetonide 0.1% cream Fluocinolone acetonide 0.025% ointment

* Potency levels are per U.S. guidelines.

† If the subject is intolerant to these TCS or they are not available, they may be substituted by a topical steroid with the same potency from the list provided in Appendix E.

‡ Low potency steroids are to be applied to sensitive areas (e.g., face, intertriginous areas, groin).

The use of wet wraps for routine application of daily TCS and/or TCIs is not allowed.

After a premature discontinuation of study drug, continuation of the step-down regimen for TCS and/or TCIs and twice-daily use of emollients will no longer be mandatory, and use of topical therapy will be per the investigator's discretion.

Rescue Therapy

Starting at the Week 4 visit, rescue treatment for AD may be provided, if medically necessary and if 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 high or super-high potency TCS (unless higher potency TCS are considered unsafe) or other alternative topical AD medications, and escalate to systemic medications only for those subjects who do not respond adequately after at least 7 days of topical treatment (Table 3).

Starting at the Week 52 visit, the use of any concomitant topical medication for AD 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.

Table 3. Potency Levels of Recommended Rescue Topical Corticosteroids*

Potency†	Recommended Topical Steroids
High	Mometasone 0.1% ointment
Very high	Augmented betamethasone dipropionate 0.05% ointment Clobetasol propionate 0.05% cream

* Potency levels are per U.S. guidelines.

† If the subject is intolerant to these TCS or they are not available, they may be substituted by a topical steroid with the same potency from the list provided in Appendix E.

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, 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 corticosteroid or 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 or the AbbVie TA MD. *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 TA MD. *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 TA MD. *Note: Intentional/prospective deviations from the protocol are not allowed. See Section 5.9 Protocol Deviations.*

- Subject is noncompliant 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 noncompliant with study procedures, which would put the subject at risk for continued participation in the trial as determined by the investigator or the AbbVie TA MD. *Note: Intentional/prospective deviations from the protocol are not allowed. See Section 5.9 Protocol Deviations.*
- Subject develops a GI perforation.
- 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 subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

Information letters and provision/withdrawal of informed consent in the Netherlands will take into account the following:

- The Medical Research Involving Human Subjects Act requires national approval of separate information letters and consent forms for participants and both parents/legal guardians in an age appropriate manner
- The Medical Treatments Agreements Act which states that individuals from 16 Years of age may decide independently and have an independent right to information
- The Code of Conduct of the Dutch Association of Pediatrics regarding the definition of (premature) withdrawal of informed consent and/or discontinuation

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 (withdrawal of informed consent), 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 should come in for 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 on study treatment throughout the study for a period of up to 136 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 upadacitinib or any other therapy once the subject's participation is concluded.

5.8 Study Drug

The individual study drug information is presented in Table 4.

Table 4. 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 subjects 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.

For allowed study drug interruption, 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.

Method of Assigning Subjects to Treatment Groups

Subjects who meet eligibility criteria will be randomized in a 1:1:1 ratio to receive with concomitant TCS, either daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg or matching placebo. Randomization for the main study will be stratified by baseline disease severity (moderate [vIGA-AD 3] versus severe [vIGA-AD 4]), geographic region (US/Puerto Rico/Canada, Japan, China, and Other), and age group (adolescent [ages 12 to 17] versus adult [ages 18 to 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 the end of the 16 week DB Period, subjects in the placebo group will be re-randomized in a 1:1 ratio (main study: stratified by EASI 50 responder [Yes/No], geographic region [US/Puerto Rico/Canada, Japan, China, and Other], and age group [adolescent/adult subjects]; adolescent sub-study: stratified by EASI 50 responder [Yes/No] and by geographic region [US/Puerto Rico/Canada and Other]) to receive daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg.

At the Screening Visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the Screening Visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

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 QD 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 three treatment groups:

- Group 1: Upadacitinib 15 mg with TCS (N = 270)
- Group 2: Upadacitinib 30 mg with TCS (N = 270)

- Group 3: Placebo with TCS (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 with TCS
- Group 2: Upadacitinib 30 mg with TCS
- Group 3: Placebo with TCS

For the main study, randomization will be stratified by baseline disease severity (moderate [vIGA-AD = 3] versus 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]). 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 with TCS
- Group 5: Upadacitinib 30 mg with TCS

For the main study, the re-randomization will be stratified by EASI 50 responder (Yes/No), 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]). 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 51 subjects (17 subjects per group), with a target enrollment of approximately 30 to 51 subjects (10 to 17 subjects per group).

Enrollment in China will be capped at 51 subjects (17 subjects per group), with a target enrollment of approximately 30 to 51 subjects (10 to 17 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 AESIs 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 MD, we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on 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.

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), 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 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 as a consequence 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.

Screening and Rescreening 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 Appendix D. Laboratory values can be retested once during the screening period. If the retested 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 rescreen once following reconsent. For additional rescreening, AbbVie TA MD/Scientific Director approval is required. As appropriate, sites are encouraged to contact the AbbVie TA MD/Scientific Director to confirm if subjects should or should not be rescreened. All screening procedures with the possible exceptions noted below will be repeated during rescreening. The subject must meet all the eligibility criteria at the time of rescreening in order to qualify for the study. There is no minimum period of time a subject must wait to rescreen 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 rescreening, provided the conditions noted in the Section 5.1 (Eligibility Criteria) are met, there are no changes in the subject's medical history that would warrant retesting, 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 purified protein derivative (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 BCG 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 polymerase chain reaction 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 1 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 international normalized ratio (INR) > 1.5 OR
  - ALT or AST > 3 × ULN along with clinical signs of possible hepatitis.

In China, 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 particule 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). 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.

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.

Subjects will complete the following questionnaires (where applicable) below as specified in Appendix D. Worst Pruritus NRS, ADerm-SS daily items, ADerm-IS daily items, ADerm-SS weekly items, ADerm-IS

weekly items, SCORAD, POEM, PGIS, PGIC, PGIT, CDLQI, DLQI, EQ-5D-5L, HADS, WPAI, and DIS should be administered before any study procedures in the order listed.

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.

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 3 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.

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 Visual Analog Scale (VAS) on the electronic 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 electronic tablet at site visits throughout the study. SCORAD components A and B will not be on the electronic tablet and performed on paper worksheets and manually 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.

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.

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 AD 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.

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

AD?" Responses range from 1 = "Extremely dissatisfied" to 7 = "Extremely satisfied." The PGIT will be administered on the tablet at site visits throughout the study.

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. 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 minimum clinically important difference (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 to 16 years old. It consists of 10 questions assessing impact of skin diseases on different aspects of subject'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. Throughout this study, the CDLQI will be administered to subjects who are < 16 (12 to 15) years old at the time of the Screening Visit, and will continue to be administered to these subjects for the duration of this 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, VAS 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.

Hospital Anxiety and Depression 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 4 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 10 to arrive at a percentage. The WPAI:AD will be administered on the tablet at site visits throughout the study.

Dermatologic Intimacy Scale (DIS)

The DIS includes 18 questions that measure the impact of skin disease on intimacy over the past 2 weeks. Responses are quantified using a 5-point Likert scale (0 – not at all, 1 – somewhat, 2 – moderately, 3 – much and 4 – very much). Scores can range from 0 to 72; a higher score represents greater intimacy impairment, calculated as the sum of all item responses. The DIS will be administered on the tablet at site visits throughout the study. Throughout this study, the DIS will be administered to subjects who are ≥ 18 years old at the time of the Screening Visit.

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 5 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 Reported Outcomes.

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 Tdap.

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.

See Section 5.3 (Prohibited Medications and Therapy) for a list of commonly used live vaccines that are prohibited during study participation.

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.

Tuberculosis Testing

The TB tests provide 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. Expert consultation for the evaluation and/or management of TB may be considered per investigator discretion.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form 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). The site staff will complete the TB risk assessment form and enter the data into the appropriate eCRF. The TB test and latent 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 MD. 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.

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 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

CXR (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 chest x-ray 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.
- Annually after Week 52 for subjects with newly identified TB risk factors as identified by the TB risk assessment form, 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).

Subjects can have a repeat CXR 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 CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, 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 CXR 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.

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

Tanner Staging (also known as the Tanner Scale) is a validated measure used in clinical practice and clinical trials to assess physical development. 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 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.

Clinical Laboratory Tests

Blood and urine samples will be collected following a minimum 8-hour fast. If a subject is not able to fast when necessary (except during Screening Visit), 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">Serum pregnancy test
HBs Ag
HBs Ab
HBc Ab
HBV DNA PCR reflex only
HCV Ab
HCV RNA reflex only
HIV
QuantiFERON-TB Gold test
hs-CRP
FSH[b]
Total IgE
Urine drug screen

<u>Local Lab Tests:</u>
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; 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 for female subjects ≤ 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 per local/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 postbaseline 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 must be discontinued;
  - Negative, the subject can continue in the trial;
  - Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can continue in the study (unless prohibited locally) 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:

- hepatitis B surface antigen (HBs Ag)
- hepatitis B core antibodies (HBc Ab)/anti-hepatitis B core antibodies (HBc)
- hepatitis B surface antibody (HBs Ab)/anti-hepatitis B surface antibody (HBs)

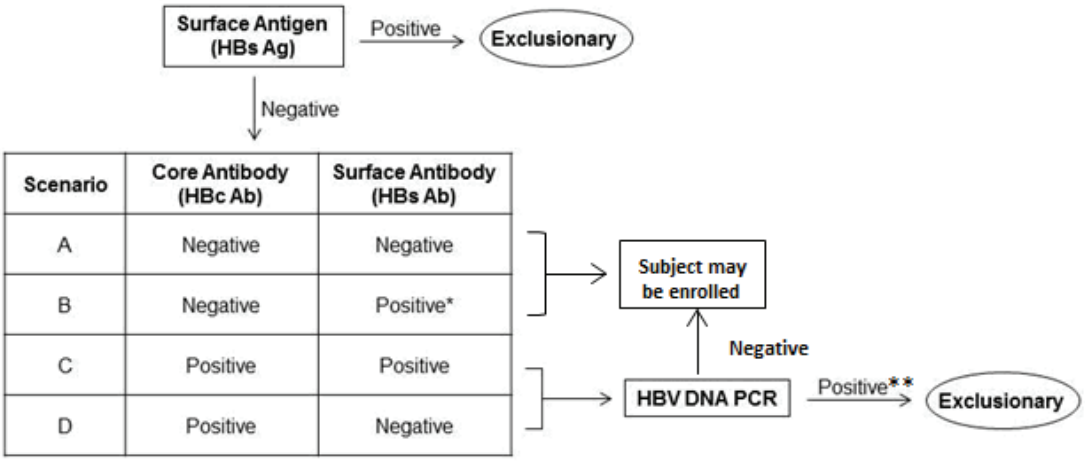
A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will trigger 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 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, the HBV DNA PCR qualitative testing is not required 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 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.
- 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; 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).

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.

Discontinuation of Study Drug and Subject Withdrawal from 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 or not 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 Appendix D, and adhere to all study procedures except for dispensing study drug and PK sample collection. 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.

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 of 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.

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 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 preplanned prior to study entry. Elective surgery will not be allowed during the study until the primary endpoint has been assessed (Week 16). 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) Adverse Event eCRF MI and Unstable Angina Adverse Event eCRF Heart Failure Adverse Event eCRF Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF Embolic and Thrombotic Event (Non-Cardiac, Non-CNS) eCRF
Herpes Zoster Infection	Herpes Zoster Adverse Event 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

If an AE meets any of the following criteria, it is to be reported to AbbVie or contract research organization (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 Reaction (SUSAR) 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 AESIs 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
- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system)

Adverse Event Severity and Relationship to Study Drug

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

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

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)
Severe (Grade 3 to 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

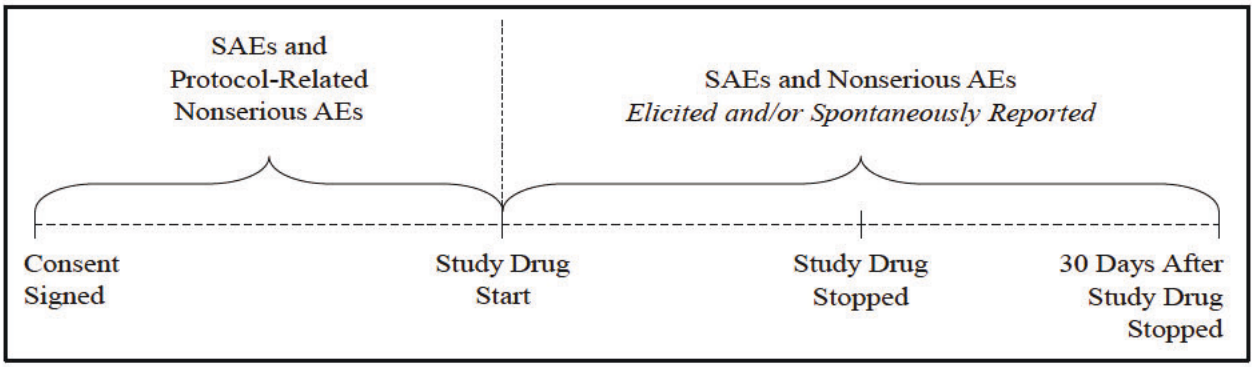
Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5).

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 SAE 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 drug 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 MACE will be collected, if applicable.

Recording Data and Analyses of Safety Findings

Adverse event will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with TEAEs (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days or 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. Serious adverse event that occur prior to the site having access to the RAVE system, or if RAVE is not operable, should be documented on the SAE nonCRF 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 Immunology Safety Team at:

Immunology Safety Team Dept. R48S, Bldg. AP31-2
1 North Waukegan Road North Chicago, Illinois 60064
Office: +1 (847) 938-8737
Email: GPRD_SafetyManagement_Immunology@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:

Office:
Mobile:
Email:
[redacted]

In emergency situations involving study subjects when the primary TA MD 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 MD:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for 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 perforation, cardiovascular events, 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 or a serious opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

Management of 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. If the diagnosis of GI perforation is confirmed, the subject must be 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 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 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 the 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 5 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 5, the repeat testing must occur as soon as possible.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, 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. • Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
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 appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from baseline).
	• Interrupt study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample.
	• 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:
	  • 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. The investigator should contact the AbbVie TA MD to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found. For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRFs.

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 x baseline value and ≤ ULN. • If confirmed serum creatinine ≥ 2 mg/dL, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete the appropriate supplemental renal eCRFs.

Laboratory Parameter	Toxicity Management Guideline
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.

Ab = antibody; ALC = absolute lymphocyte counts; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; eCRF = electronic case report form; HB = hepatitis B; 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 CAC 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 AD should be reported as an AE.

6.5 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the 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 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 assess the efficacy and safety of upadacitinib combined with TCS 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. Upadacitinib group refers to the upadacitinib with TCS, and placebo group refers to placebo with TCS.

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. 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 versus 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 the continuous variables. This handling also will be applied to selective additional endpoints (i.e., primary and key secondary variables evaluated at visits from Week 16 to Week 52) in the Blinded Extension Period.

Assessments of long-term efficacy (across the DB Period and the Blinded Extension Period) for subjects who stay on treatment will also 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.

Primary Analysis of Efficacy

The co-primary endpoints for the Primary Analysis of 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 versus 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 15 mg with concomitant use of TCS, upadacitinib 30 mg with concomitant use of TCS, or placebo with concomitant use of TCS 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 24%, and vIGA-AD 0 or 1 with at least a 2-point reduction response rate of 13% in the topical treatment with placebo arm, this sample size will also provide more than 90% power to detect the treatment differences of 38% and 20%, respectively, in 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), adding the estimation of topical treatment effect which is also based on the difference between the mono- and combo-therapy (CHRONOS) studies in dupilumab. The graphic approach for controlling multiplicity will be outlined in the SAP.

Additional adolescent subjects will be enrolled in the adolescent sub-study and randomized to upadacitinib 15 mg with concomitant use of TCS, upadacitinib 30 mg with concomitant use of TCS, or placebo with concomitant use of TCS 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.

Adverse events 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 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, and 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 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 nonlinear mixed-effects modeling approach with NONMEM 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 nonlinear 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 nonlinear relationships of primary PK parameters with various covariates will be explored.

For the same subjects from whom the PK data 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 PK 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 clinical study report.

Additional analyses will be performed if useful and appropriate.

7.6 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.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data

are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

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 PRO 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 (Individual Treatment Period Visit Activities). The ePRO data of CDLQI, DLQI, HADS, POEM, PGIS, PGIT, PGIC, EQ-5D-5L, WPAI:AD, DIS, 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 (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.

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
Ab	Antibody
AD	Alzheimer disease
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
AE(s)	adverse event(s)
AESI	adverse events of special interest
ALC	Absolute lymphocyte counts
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
BCG	bacilli Calmette-Guérin
BSA	body surface area
CAC	Cardiovascular Adjudication Committee
CD	Crohn's disease
CDLQI	Children's Dermatology Life Quality Index
CL/F	oral clearance
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CXR	chest x-ray
CYPs	cytochrome P450s
DB Period	double-blind treatment period
DIS	Dermatologic Intimacy Scale
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQ-VAS	EQ visual analogue scale

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
HBc	hepatitis B core antibodies
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
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
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model with repeated measures
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NRS	numerical rating scale
PCR	polymerase chain reaction

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
PP_M	Per-Protocol Population for the main study
PRO	patient-reported outcome
PT	preferred term
QD	Once daily
QTcF	Fridericia-corrected QT interval
RA	rheumatoid arthritis
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	Scoring atopic dermatitis
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
TPPA	Treponema pallidum particule agglutination assay
TRUST	Toluidine Red Unheated Serum Test
TSS-7	7-item total symptom score
TSS-11	11-item total symptom score
ULN	upper limit of normal
US	United States
UV	ultraviolet
V/F	apparent volume of distribution
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis

WBC	white blood cell
WPAI:AD	Work Productivity and Activity Impairment Index: Atopic Dermatitis

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-047: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 29 April 2020

Clinical research studies sponsored by AbbVie are subject to the ICH 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 IRB/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]		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development
		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.

Study Activities Table

Activity (time point clarifications in parentheses)	Screening	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64 to Wk 136 (Every 12 Wks)	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)	✓											✓	✓			
Review and document pregnancy avoidance recommendations with females of childbearing potential		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PRO																
Worst Pruritus NRS, ADerm-SS, ADerm-IS (Hand held device through Week 16. Week 16 and future visits should be on tablet)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
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)		✓					✓				✓	✓	✓		✓	

Activity (time point clarifications in parentheses)	Screening	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64 to Wk 136 (Every 12 Wks)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1														
DIS (adults only [≥ 18 years old] and every 24 weeks after Week 52)		✓			✓		✓					✓	✓		✓	
SCORAD (patient-reported items)		✓	✓				✓					✓		✓	✓	
PGIS, PGIC (except Baseline), PGIT		✓	✓	✓		✓	✓		✓	✓	✓	✓	✓		✓	
Subject hand-held device review (dispense at Screening)		✓	✓	✓	✓	✓	✓									
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)		✓	
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator Assessments: EASI, BSA, and vIGA-AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigator Assessments: SCORAD		✓	✓				✓					✓		✓	✓	
Chest x-ray (annually starting Week 52 if newly positive TB test results, newly identified TB risk factors, or subject living in endemic areas)	✓											✓	✓			

Activity (time point clarifications in parentheses)	Screening	Baseline D 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64 to Wk 136 (Every 12 Wks)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
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 potential)	✓															
hsCRP, clinical chemistry, hematology, urinalysis	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓(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 52 weeks)	✓											✓	✓			
HIV, HBV, and HCV	✓															
Blood samples for upadacitinib PK assay (PK samples will be collected from subjects at select sites)			✓		✓	✓	✓								✓	
Total IgE		✓					✓					✓				
Urine drug screen	✓															
Optional biomarker: whole blood for pharmacogenetic DNA		✓														

Activity (time point clarifications in parentheses)	Screening	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 52	Wk 64 to Wk 136 (Every 12 Wks)	Unscheduled Visit for Rescue Treatment	PD Visit	30-Day F/U Visit
		D 1														
℞ 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; D = day; DIS = Dermatologic Intimacy Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; 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; 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; PRO = patient-reported outcome; SCORAD = Scoring atopic dermatitis; TB = tuberculosis; vIGA-AD = validated Investigator Global Assessment atopic dermatitis; Wk = week; WPAI:AD = Work Productivity and Activity Impairment Index: Atopic Dermatitis

APPENDIX E. RELATIVE POTENCIES OF TOPICAL CORTICOSTEROIDS

Table V. Relative potencies of topical corticosteroids

Class	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

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Includes representative examples and not all available agents.

Additionally, use of the following topical corticosteroid will be permitted:

Low potency: prednisolone 0.5%

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Version

Protocol	Date
Version 1.0	04 May 2018
Version 1.01 VHP	20 August 2018
Version 1.02 Canada	07 August 2018
Version 2.0	18 December 2018
Administrative Change 1	30 January 2019
Version 3.0	23 July 2019
Version 4.0	02 October 2019

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

Summary of Protocol Changes:

- Section 2.2, Benefits and Risks to Subjects:
  - Clarified the statement regarding the risk to the pregnancy of female partners of male subjects who are treated with upadacitinib.

  Rationale: Updated for consistency across protocols for the upadacitinib clinical program.
- Section 3.3, Secondary Endpoints, Key Secondary Endpoints for EU/EMA and US/FDA regulatory purposes, the following clarification was made:
  - Added 'Worst' to Pruritus NRS endpoints.

  Rationale: Clarification.
- Section 3.3, Secondary Endpoints, the following key secondary endpoint for EU/EMA and US/FDA regulatory purposes was moved to Section 3.4, Additional Endpoints:
  - Proportion of subjects achieving vIGA-AD of 0 with a reduction from Baseline of ≥ 2 points.

  Rationale: This endpoint was moved to additional endpoints to minimize redundancy with other Key Secondary Endpoints and streamline Type I Error control.
- Section 3.4, Additional Endpoints, the following clarifications were made:
  - MCID estimates were added for ADerm-SS/IS endpoints.

  Rationale: To pre-specify the thresholds for the minimal clinically important differences for these outcome measures.
- Section 3.4, Additional Endpoints, the following clarifications were made:
  - Added 'for subjects with Worst Pruritus NRS > 1 at Baseline' to the Proportion of subjects achieving Worst Pruritus NRS of 0 or 1 endpoint.

- Added 'for subjects with EASI ≤ 65.4 at Baseline' to the Proportion of subjects experiencing a flare endpoints.
- Added 'for subjects with ADerm-SS skin pain score > 0 at Baseline' to the Proportion of subjects achieving ADerm-SS skin pain score of 0 endpoint.
- Added 'for subjects with POEM sleep item score > 0 at Baseline' to the Proportion of subjects achieving POEM sleep item score of 0 endpoint.
- Added 'for subjects with DLQI score > 1 at Baseline' to the Proportion of subjects ≥ 16 years old at screening achieving DLQI score of 0/1 endpoint.
- Added 'for subjects with CDLQI score > 1 at Baseline' to the Proportion of subjects < 16 years old at screening achieving Children's Dermatology life Quality Index (CDLQI) score of 0/1 endpoint.

Rationale: Clarification.

- Section 3.4, Additional Endpoints, the following endpoints were added:
  - Proportion of subjects achieving EASI 50 at Week 2;
  - 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;
  - Percent change in Scoring Atopic Dermatitis (SCORAD) from Baseline at Week 16;
  - Proportion of subjects achieving EASI 50;

  Rationale: It is necessary for compliance with the Paediatric Investigational Plan.
- Section 3.4, Additional Endpoints, the following clarification was made to the Note:

  "Days from the start of systemic rescue will not be considered as TCS-free days."

  Rationale: Clarification
- Section 4.1, Overall Study Design and Plan and Section 7.1, Statistical and Analytical Plans the following was added:

  "In addition, a Week 52 analysis of the main study will be performed after all ongoing subjects complete the Week 52 visit."

  Rationale: Week 52 interim analysis of the main study added to the protocol to fulfill a regulatory requirement.
- Section 5.1 Eligibility Criterion 10: "(refer to Section 5.10 for details)" was added.

  Rationale: Updated for consistency across protocols for the upadacitinib clinical program.
- Section 5.1 Eligibility Criterion 23: clarified the following 'History of gastrointestinal (GI) perforation (other than due to appendicitis or mechanical injury), diverticulitis or significantly increased risk for GI perforation per investigator judgment;'

  Rationale: Updated for consistency across protocols for the upadacitinib clinical program.

- Section 5.3, Prohibited Medications and Therapy, Topical Therapy subjection:
  - Revised the following statement of 'Topical anti-infectives, topical antihistamines, and bleach baths may be used in the first 16 weeks of the study if they were used in the 6 months prior to the Screening visit and are allowed per investigator discretion for the remainder of the study.' to '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.'

  Rationale: Updated to clarify this is meant for treatments of AD.
- Section 5.4, Prior and Concomitant Therapy, Rescue Therapy subsection:
  - Added "compared to the Baseline EASI score" to both parameters.

  Rationale: Clarification.
- Section 5.5, Withdrawal of Subjects and Discontinuation of Study
  - Updated the study drug discontinuation criteria:
    - 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.

  Rationale: Help clarify permanent discontinuation from study drug criteria.
- Added discontinuation criterion to Section 5.5, Withdrawal of Subjects and Discontinuation of Study.
  - "Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurological arterial thrombosis."

  Rationale: Added an additional safety precaution for subjects, given the recent concerns raised for the JAK inhibitor class regarding the risk of thromboembolic events.
- Section 6.1, Complaints and Adverse Events, Adverse Events of Special Interest
  - Add "Active" to Tuberculosis
  - Add "Adjudicated" to Gastrointestinal perforations

  Rationale: Active TB is an identified risk for JAK inhibitors including upadacitinib. Given the clinical importance of active TB, it is being monitored and managed more intensively. According, latent/active TB as an AESEI is changed to active TB. GI perforation is a potential risk for upadacitinib therapy. The concern of this risk is the development of spontaneous perforation during the therapy. The sponsor has set up an internal adjudication process and the evaluation will be based on the adjudicated events.

- Section 6.1, Complaints and Adverse Events
  - Added the Eczema herpeticum eCRF.

  Rationale: To collect additional information in order to better characterize this event that occurs more often in the AD population.
- Updated Section 6.2 Toxicity Management, Management of Thrombosis Events with the following:
  - "If the diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurological arterial thrombosis is confirmed, the subject must be discontinued from study drug."

  Rationale: Added an additional safety precaution for subjects, given the recent concerns raised for the JAK inhibitor class regarding the risk of thromboembolic events.
- Updated Section 6.2 Toxicity Management, Management of Thrombosis Events with the following:
  - Removed the Management of Muscle-Related Events statement.

  Rationale: The study is still monitoring CPK and as such this text is not required.
- Updated Section 6.2 Toxicity Management, Table 5 Specific Toxicity Management Guidelines for Abnormal Laboratory Values, AST or ALT parameter column.
  - Clarified toxicity management criteria related to ALT and AST.
  - Added abbreviations to the bottom of the table.

  Rationale: Clarification.
- Updated Section 7.1, Statistical and Analytical Plans: Add additional analysis at Week 52 for main study to support the regulatory submission and add the further clarification when to have the primary analysis of adolescent sub study.

  Rationale: Clarification.
- Updated Section 7.3, Statistical Analyses for Efficacy: 1) Clarify the stratification factors in the analysis of main study and the analysis of adolescent. 2) Clarify that the primary analysis of efficacy will be conducted in the ITT_M Population.

  Rationale: Clarification.

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

- Minor text edits as needed for consistency and clarity.
- Added abbreviations under Table 5.
- Updated list of protocol signatures.

Summary of Operations Manual Changes:

None.

APPENDIX G. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M16-047 – AD Up

Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids 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 Combination with Topical Corticosteroids in Adolescent and Adult Subjects with Moderate to Severe Atopic Dermatitis

1 CONTACTS

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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 Email: sample.receiving@abbvie.com

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TABLE OF CONTENTS

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2 PROTOCOL ACTIVITIES BY VISIT

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.

SCREENING

INTERVIEWS & QUESTIONNAIRES	• Subject information and informed consent • 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), and validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) • 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)

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 Depression Scale (HADS)	• EuroQol Dimensions 5 Levels (EQ-5D-5L) • Work Productivity and Activity Impairment Index: Atopic Dermatitis (WPAI-AD) • Dermatologic Intimacy Scale (DIS) (adults only [≥ 18 years old]) • Patient Global Impression of Severity (PGIS)/Treatment (PGIT) • Subject hand-held device review
EXAM	• Height • Body weight • Vital signs • Physical exam • AE assessment	• Investigator assessments: EASI, BSA, vIGA-AD, and SCORAD (patient-reported items) • Tanner Staging (adolescent subjects only)
LOCAL LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology • Urinalysis	• Total immunoglobulin E (IgE) • Optional biomarker: whole blood for pharmacogenetic DNA
TREATMENT	• Randomization/drug assignment	• Dispense study drug

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

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.

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, Patient Global Impression of Change (PGIC), PGIT • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator assessments: EASI, BSA, vIGA-AD, and SCORAD (patient-reported items)
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology	• Urinalysis • Blood samples for upadacitinib pharmacokinetic (PK) assay (PK samples will be collected from subjects at select sites)

WEEK 4:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst pruritus NRS • ADerm-SS • ADerm-IS	• EQ-5D-5L • PGIS, PGIC, PGIT • Subject hand-held device review
EXAM	• Body weight • Vital signs • AE assessment	• Investigator assessments: EASI, BSA, and vIGA-AD
LOCAL LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• hsCRP • Clinical chemistry	• 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 • ADerm-SS • ADerm-IS • CDLQI or DLQI	• POEM • DIS • Subject hand-held device review
EXAM	• Height (adolescent subjects only) • Body weight • Vital signs • AE assessment	• Investigator assessments: EASI, BSA, and vIGA-AD
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)
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 • ADerm-SS • ADerm-IS	• HADS • PGIS, PGIC, PGIT • Subject hand-held device review
EXAM	• Body weight • Vital signs • AE assessment	• Investigator assessments: EASI, BSA, and vIGA-AD
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)
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 • DIS • PGIS, PGIC, PGIT • Subject hand-held device review and return
EXAM	• Height (adolescent subjects only) • Body weight • Vital signs • Physical exam • AE assessment	• Investigator assessments: EASI, BSA, vIGA-AD, and SCORAD (patient-reported items) • Tanner Staging (adolescent subjects only)
LOCAL LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology • Urinalysis • Total IgE	• Blood samples for upadacitinib PK assay (PK samples will be collected from subjects at select sites)
TREATMENT	• Dispense study drug	

WEEK 20:

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

WEEK 64 to Week 136 (Every 12 Weeks):

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 • CDLQI or DLQI • POEM	• HADS • EQ-5D-5L • WPAI:AD • DIS • PGIS, PGIC, PGIT
EXAM	• Height (adolescent subjects only) • Body weight • Vital signs • Physical exam • AE assessment	• Investigator assessments: EASI, BSA, and vIGA-AD • Chest x-ray (Week 100) • Tanner Staging (adolescent subjects only) • 12-lead ECG (Week 100 only)
LOCAL LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	• Dispense urine pregnancy tests for monthly home testing
CENTRAL LAB	• hsCRP • Clinical chemistry • Hematology	• Urinalysis • TB test
TREATMENT	• Dispense study drug	

NOTES:
- Visits are every 12 weeks after the Week 52 visit up to Week 136 (Weeks 64, 76, 88, 100, 112, 124, and 136).
- CDLQI, DLQI, POEM, HADS, EQ-5D-5L, WPAI:AD, DIS (adults only), Tanner Staging (adolescents only), and physical exam will be performed every 24 weeks after the Week 52 visit (Weeks 76, 100, and 124). Once a subject reaches stage 5 in both categories, Tanner Staging will no longer need to be assessed for that subject.
- Chest x-ray should be performed annually after Week 52 if newly positive TB results.
- 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.
- Week 104 procedures should be completed at the Week 100 Visit.

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 • ADerm-SS • ADerm-IS	• SCORAD (patient-reported items; if visit occurs prior to Week 52) • CDLQI or DLQI • POEM
EXAM	• Body weight • Vital signs • AE assessment	• Investigator assessments: EASI, BSA, SCORAD (patient-reported items; if visit occurs prior to Week 52), and vIGA-AD
LOCAL LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• hsCRP • Clinical chemistry	• Hematology • Urinalysis

NOTES: After an unscheduled rescue visit, subjects will continue to follow the standard protocol visit schedule, as applicable.

PD Visit: ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ○ ● ○

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; if PD visit occurs prior to Week 52) • CDLQI or DLQI	• POEM • HADS • EQ-5D-5L • WPAI-AD • DIS • PGIS, PGIC, PGIT
EXAM	• Height (adolescent subjects only) • Body weight • Vital signs • Physical exam • AE assessment • ECG	• Investigator assessments: EASI, BSA, vIGA-AD, and SCORAD (patient-reported items; if PD visit occurs prior to Week 52) • Tanner Staging (adolescent subjects only)
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)

30-Day Follow-up Visit:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy
EXAM	• Body Weight • Vital Signs • Physical Exam • AE assessment
CENTRAL LAB (as needed for ongoing AEs)	• hsCRP • Clinical Chemistry • Hematology • Urinalysis

NOTES: The 30-day follow-up visit is 30 days after last dose of study drug.

For those subjects who prematurely discontinue the study a 30-day follow-up visit to assess the health of the subject at study completion and 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 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 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, and PK sample collection. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply.

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
DIS	Dermatologic Intimacy Scale
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EQ-5D-5L	EuroQol Dimensions 5 Levels
HADS	Hospital Anxiety and Depression Scale
NRS	Numerical Rating Scale
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGIT	Patient Global Impression of Treatment
POEM	Patient-oriented Eczema Measure
SCORAD	Scoring atopic dermatitis
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 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 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable pain ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
6. During the past 24 hours, how bad was your **worst dry skin** due to AD?	No dry skin 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable dry skin ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
7. During the past 24 hours, how bad was your **worst skin flaking** due to AD?	No flaking 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable flaking ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8. During the past 24 hours, how bad was your **worst rash (redness, blisters, bumpy skin)** due to AD?	No rash 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable rash ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
9. During the past 24 hours, how bad was your **worst skin thickening** due to AD?	No skin thickening 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable skin thickening ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
10. During the past 24 hours, how bad was your **worst bleeding** due to AD?	No bleeding 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable bleeding ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
11. During the past 24 hours, how bad was your **worst skin oozing** due to AD?	No oozing 0 1 2 3 4 5 6 7 8 9 10 Worst imaginable oozing ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

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 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

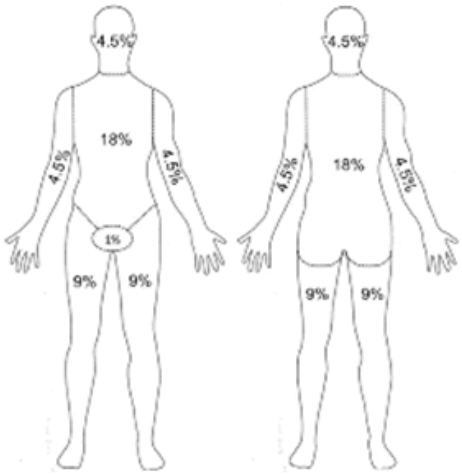
AD Impact Scale (ADerm-IS)-English-USA-V2

3.5 SCORING ATOPIC DERMATITIS (SCORAD) EXAMPLE

M16-047: 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 M16-047 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)

3.6 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

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.

3.7 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.

3.8 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**

3.9 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**

3.10 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.

3.11 CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX (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?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school Very much Quite a lot Only a little Not at all 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.

3.12 EUROQOL DIMENSIONS 5 LEVELS (EQ-5D-5L) EXAMPLE

EQ-5D-5L	
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
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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.*	

3.13 HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

GL assessment

Hospital Anxiety and Depression Scale (HADS)

Name: _____ Date: _____

FOLD HERE

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

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

Now check that you have answered all the questions

	A	D
TOTAL		

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

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)

3.15 DERMATOLOGIC INTIMACY SCALE (DIS) EXAMPLE

Subject: *Total Score:* _____/__72___
Date:

Dermatologic Intimacy Scale (D.I.S.)

Please answer the following questions in regards to your skin over the past 2 weeks.

	Not at all	Somewhat	Moderately	Much	Very much
1) I fear rejection due to my skin condition	0	1	2	3	4
2) I conceal my skin condition from my partner/potential partner	0	1	2	3	4
3) I am worried about how my partner/potential partner views my skin	0	1	2	3	4
4) My skin condition affects my ability to emotionally connect with my partner/potential partner	0	1	2	3	4
5) I am conscious of my skin when in social and romantic situations	0	1	2	3	4
6) My skin condition affects the attire I choose to wear to social and romantic events	0	1	2	3	4
7) My skin condition prevents me from meeting new people	0	1	2	3	4
8) My skin condition discourages me from seeking or accepting a social or romantic invitation	0	1	2	3	4
9) My skin disease causes me to fear social interaction with men and/or women of interest to me	0	1	2	3	4
10) My skin condition makes me less attractive and desirable to others	0	1	2	3	4
11) I am less outgoing due to my skin condition	0	1	2	3	4
12) I am uncomfortable being nude as a result of my skin condition	0	1	2	3	4
13) I do not like when my partner/ potential partner touches my skin	0	1	2	3	4
14) My skin condition is socially and/or romantically isolating	0	1	2	3	4
15) My skin significantly affects the quality of my social and romantic relationships	0	1	2	3	4
16) My partner/potential partner is unable to appreciate the impact that my skin condition has on my life	0	1	2	3	4
17) My skin causes me to have a negative outlook on the future with my partner/potential partner	0	1	2	3	4
18) I am anxious about romantic encounters due to my skin condition	0	1	2	3	4

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.

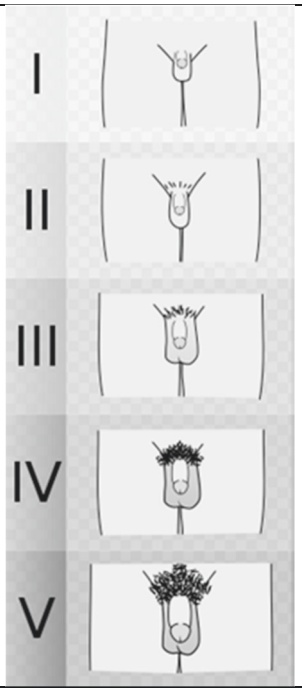
3.18 TB RISK ASSESSMENT FORM EXAMPLE

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