abbvie

Protocol for Study M16-046 – Heads Up

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

VERSION:	1.0	DATE:	17 October 2018
SPONSOR:	For Non-EU Countries:* AbbVie Inc. For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie)	NUMBER OF SITES:	Up to 160
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EUDRACT:	2018-002264-57

FULL TITLE: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

Sponsor contact for all non-emergency issues:

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

Office: [redacted]
Mobile:
Email:

Sponsor emergency contact:

[redacted]

AbbVie Inc.
1500 Seaport Boulevard
Redwood City, CA 94063

Office: [redacted]
Mobile:
Fax:
Email:

EMERGENCY 24-hour Number [redacted]

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

abbvie

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in 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. AbbVie is developing a small molecule inhibitor of JAK, upadacitinib, that may address the current needs for subjects with AD. The second generation of JAK inhibitors, with different selectivity profiles against JAK1, JAK2, JAK3, and Tyrosine kinase 2 (Tyk2), is in development. Upadacitinib (ABT-494) is a novel selective JAK1 inhibitor being developed for rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), axial spondyloarthritis (AxSpA), Giant Cell Arteritis, 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 over available therapies. Results from the Phase 2 study in AD showed that upadacitinib doses of 15 mg and 30 mg per day had an efficacy and safety profile that can benefit patients with moderate to severe AD.
Objective(s) and Endpoint(s):	The objective of this study is to evaluate the efficacy and safety of upadacitinib versus dupilumab for the treatment of adult subjects with moderate to severe AD who are candidates for systemic therapy. The primary endpoint is the proportion of subjects achieving a 75% reduction in Eczema Area and Severity Index (EASI 75) at Week 16.
Investigator(s):	Multicenter; investigator information on file at AbbVie.
Study Site(s):	Up to 160 sites globally
Study Population and Number of Subjects to be Enrolled:	Approximately 650 adults subjects with moderate to severe AD who are candidates for systemic therapy.
Investigational Plan:	This is a Phase 3b, randomized, double-blind, double-dummy, active comparator-controlled multicenter study.
Key Eligibility Criteria:	Demographics • Subject must be ≥ 18 years old and ≤ 75 years old AD Disease Activity • Subject has chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria during screening and baseline; • Subject meets all of the following disease activity criteria:

	• EASI score ≥ 16 at the Screening and Baseline Visits; • Validated Investigator Global Assessment for atopic dermatitis (vIGA-AD) score ≥ 3 at the Screening and Baseline Visits; • ≥ 10% body surface area (BSA) 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. • Subject has a documented history (within 6 months of the Baseline Visit) of inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) • OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, • OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks). Prior/Concomitant Therapy • No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, PF-04965842, and filgotinib). • No prior exposure to dupilumab. • Subjects must not have used the following AD treatments within the timeframe specified below 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 Section 5.3) 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), 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 ratio to receive an active agent (upadacitinib or dupilumab) and the placebo of the other agent until the Week 24 visit: • Upadacitinib 30 mg tablets + placebo pre-filled syringe; OR • Dupilumab 300 mg + placebo tablet
Date of Protocol Synopsis:	17 October 2018

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Atopic dermatitis (AD) is an inflammatory, pruritic, chronic or chronically relapsing skin disease. The adult phase of AD begins at puberty and frequently continues into adulthood. In adults, disease typically involves flexural folds, face, neck, upper arms and back, and dorsal surfaces of the hands and feet.[1,2]

Management of AD primarily consists of trigger avoidance, careful attention to skin care, and both pharmacologic and nonpharmacologic treatment.[3] The 2006 PRACTALL Consensus Report recommends treatment by addition of agents in a stepwise fashion based on disease severity, starting with topical corticosteroids of increasing potency and/or a topical calcineurin inhibitor and escalating to systemic therapy for recalcitrant, severe disease.[4] Systemic immunomodulatory agents used to treat AD include cyclosporin A, azathioprine, methotrexate (MTX), mycophenolate mofetil, interferon gamma, systemic corticosteroids, and dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling.[5-7] Despite these systemic therapies, an unmet need continues to exist for patients who are non-responders or partial responders to these agents.

The Janus kinases or JAKs are a family of intracellular tyrosine kinases that function as dimers in the signaling process of many cytokine receptors. The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases. Targeting the JAK signaling pathway for AD is supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of AD. The activation of JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to AD and other inflammatory disorders.[8,9]

Upadacitinib is an oral, reversible JAK1 selective inhibitor. JAK1 inhibition blocks the signaling of many important pro-inflammatory cytokines, including IL-2, IL-6, IL-7, and IL-15, which are known contributors to inflammatory disorders. Through modulation of these proinflammatory cytokine pathways, upadacitinib offers the potential for effective treatment of inflammatory and autoimmune disorders such as AD, rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), axial spondyloarthritis (AxSpA), and Giant Cell Arteritis. In the upadacitinib Phase 2 AD study, a statistically significant difference in the mean percent change from Baseline in EASI score at Week 16 (primary endpoint) was observed for 7.5 mg (–39.4%; $P = 0.032$ vs placebo), 15 mg (–61.7%; $P < 0.001$ vs placebo), and 30 mg (–74.4%; $P < 0.001$ vs placebo) groups compared with placebo (–23.0%). Through Week 16 (Period 1), the percentages of subjects with adverse events (AEs), serious adverse events (SAEs), severe AEs, and AEs leading to discontinuation were similar across treatment groups. There were no deaths reported during Period 1.

Additionally, upadacitinib was studied in rheumatoid arthritis with the results of two Phase 2 studies and two Phase 3 studies available as peer-reviewed manuscripts.[10-13] Results from the Phase 2 study in AD showed that upadacitinib doses of 15 mg and 30 mg per day had an efficacy and safety profile that can benefit patients with moderate to severe AD.

Clinical Hypothesis

Based on the differentiated selectivity profile for JAK1 inhibition, upadacitinib could demonstrate an improved benefit-risk profile compared to other therapeutic strategies for patients with inflammatory diseases.

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

Additional information regarding indications under study can be found in the current edition of the upadacitinib Investigator's Brochure.[14]

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.[15]

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.[5] 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 IL-4 and IL-13 signaling, was approved for the treatment of moderate to severe AD in adults in the European Union (EU)[16] and United States (US)[17] in 2017. 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 topical corticosteroids [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.[6,7] Nearly 50% of dupilumab subjects who were IGA 0 or 1 responders at Week 16 became nonresponders by Week 52.[16]

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 currently available agents.

Upadacitinib is a novel selective orally available JAK1 inhibitor with the potential to decrease Th2 mediated skin inflammation and itch while having minimal inhibitory effects on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.[18,19]

Primary results from the ongoing Phase 2 study demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected doses for Phase 3 (15 mg and 30 mg once daily [QD]) compared

to placebo in subjects with moderate to severe AD. Taken together, the efficacy and safety data from the Phase 2 AD study and cumulative safety data from ongoing Phase 2 and 3 programs in other disease indications support further development of upadacitinib in subjects with moderate to severe AD.

Adverse events such as infections, herpes zoster reactivation, malignancies, and hematologic AEs have been observed with JAK inhibition. The safety profile specific to upadacitinib is evolving, with safety results to date consistent with those known to be associated with JAK inhibition, with non-serious infections (e.g., upper respiratory tract infection or nasopharyngitis) being the most commonly reported AEs. In addition, laboratory changes observed with upadacitinib include elevations of serum transaminases, lipids, creatinine, and creatine phosphokinase; both increased and reduced hemoglobin, depending on Baseline inflammatory burden; and reductions in white blood cell counts, including natural killer (NK) cells.

The results of all genetic toxicology testing indicate that upadacitinib is not genotoxic; however, upadacitinib may be teratogenic, which necessitates avoidance of pregnancy in females of childbearing potential. Based on an embryo fetal development study in rats, there is judged to be no risk associated with administration of upadacitinib to male partners of females of childbearing potential.

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.[10]

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

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to evaluate the efficacy and safety of upadacitinib versus dupilumab for the treatment of adult subjects with moderate to severe atopic dermatitis who are candidates for systemic therapy.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving a 75% reduction in EASI (EASI 75) from Baseline at Week 16.

3.3 Secondary Endpoints

Ranked Secondary Endpoints:

1. Percent change from Baseline to Week 16 in worst pruritus numerical rating scale (NRS)
2. Proportion of subjects achieving a 100% reduction in EASI (EASI 100) at Week 16
3. Proportion of subjects achieving a 90% reduction in EASI (EASI 90) at Week 16

3.4 Additional Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all visits other than Week 16. In addition, the following variables will be analyzed at all visits:

- Proportion of subjects achieving an improvement (reduction) in worst pruritus NRS ≥ 4 from Baseline
- Proportion of subjects achieving 75% reduction in EASI in the head and neck body region from Baseline
- Proportion of subjects achieving 75% reduction in EASI in each body region (other than head and neck) from Baseline

3.5 Safety Endpoints

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

3.6 Biomarker Samples

Optional biospecimens (e.g., blood, serum, plasma, and skin biopsies) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. This research may be exploratory in nature and the results may not be included with the clinical study report.

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 with pharmacokinetics (drug metabolizing enzymes, drug transport proteins), genes within the target pathway (JAK, Tyk2, TNF), or other genes believed to be related to AD and other inflammatory diseases (Filaggrin [FLG], Claudin 1 [CLDN1], Human Leukocyte Antigen [HLA]). Research may also include epigenetic changes in DNA that may associate with the subject's response to treatment or disease. Samples for RNA and proteomics will be used to research if any genetic variants result in changes to gene expression or protein concentrations. For any samples collected in Germany, the research will be restricted to upadacitinib and AD.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b, randomized, double-blind, double-dummy, active comparator-controlled multicenter study that will evaluate the safety and efficacy of upadacitinib versus dupilumab in 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 within 6 months prior to the Baseline Visit or for whom topical treatments are otherwise medically inadvisable.

The study is comprised of a 35-day Screening Period, a 24-week double-blind treatment period, and an End-of-Treatment Follow-up Visit. The End-of-Treatment Follow-up Visit will be 12 weeks after the last injection.

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to one of the two arms as shown below:

- Treatment A (N = 325): Daily oral doses of upadacitinib 30 mg from the Baseline visit until the Week 24 visit, and placebo pre-filled syringe administered at the baseline visit (2 subcutaneous [SC] injections), followed by placebo pre-filled syringe (1 injection) every other week until the Week 22 visit.
- Treatment B (N = 325): Dupilumab 600 mg (2 × 300 mg dupilumab SC injection) administered at the Baseline visit, followed by dupilumab 300 mg SC injection every other week until the Week 22 visit and daily oral doses of placebo tablets from the Baseline visit until the Week 24 visit.

Randomization will be stratified by baseline disease severity (moderate validated Investigator Global Assessment for atopic dermatitis [vIGA-AD 3] vs. severe [vIGA-AD 4]) and age (< 40, ≥ 40 to < 65, ≥ 65 years). The subject's age at baseline will be used for randomization and throughout the duration of the study.

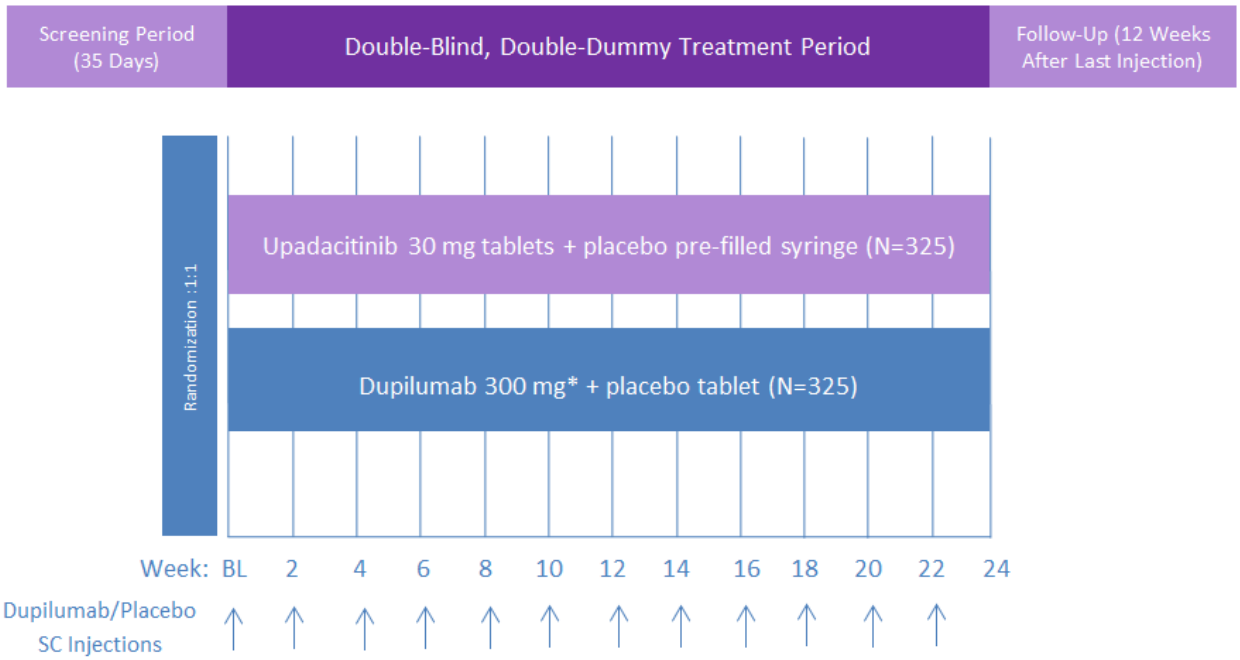
Information on the Data Monitoring Committee (DMC) and Cardiovascular Adjudication Committee (CAC) is described in Section 6.3.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in Section 5.10.

See Section 5.1 for information regarding eligibility criteria.

The study sites and subjects will remain blinded to treatment assignments for the duration of the study, and the only database lock will be performed at the end of study. No interim analysis will be conducted.

Figure 1. Study Schematic



BL = Baseline; SC = subcutaneous

* Dupilumab 300 mg SC injection will be administered every other week starting at the Week 2 visit and until the Week 22 visit, after an initial dose of 600 mg at the Baseline visit.

4.2 Discussion of Study Design

Choice of Control Group

Dupilumab is a systemic therapy approved in the US, EU, and elsewhere for treatment of adult patients with moderate to severe AD. Indirect comparison of the upadacitinib Phase 2 study results with published results from the dupilumab Phase 3 studies shows superior nominal results for upadacitinib 30 mg QD versus dupilumab 300 mg every other week, in a similar patient population. This study is being performed to evaluate the hypothesis of potential superiority of upadacitinib.

Appropriateness of Measurements

Standard clinical and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with AD. Other than the biomarker analyses which are exploratory, all clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Eligible subjects have a documented history of inadequate response to treatment with topical or systemic AD treatments or they are subjects for whom topical treatments are otherwise medically inadvisable. As a result, these subjects have an unmet need for adequate control of their AD. Results in

the Phase 2 study that evaluated upadacitinib treatment for AD demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected dose (30 mg QD) compared to placebo in subjects with moderate to severe AD. Therefore, this subject population is considered appropriate for treatment and for evaluating a treatment difference between upadacitinib and dupilumab.

Selection of Doses in the Study

This study will evaluate upadacitinib (30 mg QD). The selection of this dose was informed by the analysis of the 16-week safety, efficacy, and exposure-response data of the Period 1 of the Phase 2 AD Study M16-048, which evaluated 3 doses of upadacitinib (7.5 mg, 15 mg, and 30 mg QD) versus placebo. In addition, all of the currently available pharmacokinetic, pharmacodynamic, safety, and efficacy data from upadacitinib studies were used to support the selection of these doses.

Study M16-048 Period 1 results demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected dose (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.

In addition, indirect comparison of the Phase 2 study results with published results from the dupilumab Phase 3 studies shows superior nominal results for upadacitinib 30 mg QD versus dupilumab 300 mg every other week, in a similar patient population. This study is being performed to confirm the hypothesis of potential superiority raised by this indirect comparison.

In summary, exposures associated with upadacitinib 30 mg QD using the once-daily formulation are predicted to be efficacious in treatment of subjects with moderate to severe AD with limited effects on laboratory parameters.

The selection of the dupilumab dose was based on the approved posology in moderate to severe atopic dermatitis subjects [initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection].[16,17]

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 ≥ 18 years old and ≤ 75 years old at Screening Visit.

- 2. Subjects and/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.
- 3. Subject is judged to be in general good health (other than AD) as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

AD Disease Activity

- 4. Chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria during screening and baseline;[20]
- 5. 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 (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.
- 6. 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.
- 7. Documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or topical calcineurin inhibitors (TCI) OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).

Contraception

- 8. 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.
- 9. 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 12-weeks after the last dose of study drug.
- 10. Female subject must not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 12 weeks after the last injection.
- 11. Additional local requirements may apply. Refer to Section 5.10.

Prior and Concomitant Therapy

- 12. No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, PF-04965842, and filgotinib).
- 13. No prior exposure to dupilumab.
- 14. 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-gamma (IFN-γ) and mycophenolate mofetil within 4 weeks;
  - Targeted biologic treatments (refer to Section 5.3) within 5 half-lives [if known] or within 12 weeks, whichever is longer;
  - Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks;
  - Oral or parenteral traditional Chinese medicine within 4 weeks;
  - Marijuana use within 2 weeks;
  - Topical treatments (with the exception of topical emollient treatments, described in Eligibility Criterion 8), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days.
- 15. Subjects must not have received any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.
- 16. No systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to Table 1 in Section 5.3 for examples of commonly used strong CYP3A inhibitors and inducers).
- 17. 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.

Medical History

- 18. Laboratory values must **not** meet 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;
  - Total white blood cell count (WBC) < 2,500/µL;
  - Absolute neutrophil count (ANC) < 1,500/µL;

- Platelet count < 100,000/µL;
- Absolute lymphocyte count < 800/µL;
- Hemoglobin < 10 g/dL.

19. Subject must have no current or past history of infection including:
    - 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 or disseminated (even a single episode) herpes zoster;
    - History of disseminated (even a single episode) herpes simplex (including eczema herpeticum);
    - History of known invasive infection (e.g., listeriosis and histoplasmosis);
    - Human immunodeficiency virus (HIV) infection, defined as confirmed positive anti-HIV antibody (HIV Ab) test;
    - Active Tuberculosis (TB) or meets TB exclusionary parameters (refer to Section 5.10 for specific requirements for TB testing);
    - Non-skin related active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit;
    - Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
    - Active hepatitis B virus (HBV) or hepatitis C virus (HCV):
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects (and for hepatitis B surface antibody positive [+] where mandated per local requirements);
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).

20. Subject must have no current or past history of infection including:
    - History of any of the following cardiovascular conditions:
        - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
        - Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
    - Any other unstable clinical condition which, in the opinion of the investigator, would put the subject at risk by participating in the protocol. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
    - Subject has been a previous recipient of an organ transplant which requires continued immunosuppression;

- History of gastrointestinal (GI) perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for GI perforation per investigator judgment;
- Conditions that could interfere with drug absorption including but not limited to short bowel syndrome;
- History of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix;
- History of clinically significant medical conditions or any other reason, which in the opinion of the investigator, would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.

Miscellaneous

- 21. 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.
- 22. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.

5.2 Contraception Recommendations

Contraception Recommendations for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

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

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, 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.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)
  - Females who have not experienced menarche (at least one menstrual period)
- Females of Childbearing Potential

  Females of childbearing potential must avoid pregnancy while taking study drug and for at least 12 weeks after the last injection. Females must commit to one of the following methods of highly effective birth control:

  - Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.

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

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

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

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

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

5.3 Prohibited Medications and Therapy

JAK Inhibitors

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

Targeted Biologic Therapies

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

- abatacept
- adalimumab
- anakinra
- belimumab
- certolizumab
- efalizumab
- etanercept
- golimumab
- guselkumab
- infliximab
- ixekizumab
- natalizumab
- omalizumab
- rituximab
- secukinumab
- tocilizumab
- ustekinumab
- vedolizumab

Other Non-Biologic Systemic Therapy

Concomitant treatment with systemic non-steroidal systemic immunosuppressive drugs is prohibited during treatment with study drug, including but not limited to:

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

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

Corticosteroids

Concomitant treatment with systemic corticosteroids (oral, intravenous, intramuscular) and intralesional corticosteroids is prohibited during treatment with study drug.

Inhaled, ophthalmic drops and nasal corticosteroid formulations are allowed throughout the study.

See Rescue Therapy in Section 5.4 for further details on allowed 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 treatment with study drug.

Phototherapy, Tanning Booth, and Extended Sun Exposure

Ultra-violet (UV) B or UVA phototherapy including psoralen and ultraviolet A (PUVA) or laser therapy for at least 4 weeks prior to the Baseline visit and during the study are not allowed. 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 treatment with study drug.

Topical Therapy

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

Topical anti-infectives, topical antihistamines, and bleach baths may be used during the study only 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.

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

Vaccines

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (per local label) at least 14 days (or longer if locally required) before first dose of study drug. Live vaccinations are prohibited during study participation including at least 12 weeks after the last injection.

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.

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

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Zostavax (herpes zoster, live attenuated);

- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles-mumps-rubella-varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid (oral).

See Section 5.4 for information about permitted vaccines and recommendations for vaccines.

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.

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
Conivaptan	Phenytoin
Grapefruit (fruit or juice)	Rifampin
Indinavir	St. John's Wort
Itraconazole	
Ketoconazole	
Lopinavir/Ritonavir	
Mibefradil	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

Elective and Emergency Surgeries

Elective surgery will not be allowed during the study.

If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. See Section 5.7 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) that the subject is receiving at the time of screening, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF). Also, medications taken for atopic dermatitis since date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, route of administration.

If there are any questions regarding concomitant or prior therapies, the AbbVie TA SD should be contacted who will then discuss it with the AbbVie Therapeutic Area Medical Director (TA MD) and provide a recommendation.

Vaccines

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap). It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks before first dose of study drug or administered at least 12 weeks after the last injection. If the herpes zoster vaccine is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing 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 herpes zoster vaccine should not be administered. See Prohibited Medications/Therapy for a list of commonly used live vaccines that are prohibited during study participation.

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

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 for the duration of the study.

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.

Rescue Therapy

Rescue treatment for AD may be provided, if medically necessary at the discretion of the investigator.

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

Subjects who receive topical rescue treatment during the study treatment period can continue study drug.

If a subject needs rescue treatment with a systemic agent (including but not limited to corticosteroids, cyclosporine, methotrexate [MTX], mycophenolate mofetil, azathioprine) or phototherapy, study drug should be permanently discontinued prior to the initiation of rescue systemic agent or phototherapy.

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

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

5.5 Withdrawal of Subjects and Discontinuation of Study

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

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, gastrointestinal perforation, cardiovascular and thromboembolic events, malignancy, ECG abnormality, and select laboratory abnormalities.

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

- Rescue treatment is administered outside of the parameters described in Section 5.4 (Rescue Therapy).
- Initiation of any systemic rescue therapy for AD.
- Permanent discontinuation from study drug will be mandatory 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).
- Anaphylactic reaction or other severe systemic or local reaction to study drug injection.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator and the AbbVie TA MD or TA SD.
- 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 or TA SD.
- 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 or TA SD.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant or plans to become pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.

- Subject develops a GI perforation.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial in consultation with the AbbVie TA MD or TA SD.
- 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 a change of QT interval corrected (QTc) interval > 60 msec from baseline.

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.

5.6 Follow-Up for Subject Withdrawal from Study

Discontinuation of Study Drug and Continuation of Study Participation

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment or study participation should complete a Premature Discontinuation visit (PD visit). 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.

Subjects who prematurely discontinue study drug but continue study participation should complete a PD visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix D and should adhere to all study procedures except for dispensing study drug. 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 End-End-of-Treatment 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 12 weeks after the last injection.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, an End-of-Treatment Follow-up visit

or phone call may be completed 12 weeks after the last injection to ensure all treatment-emergent AEs and SAEs have been resolved.

Biomarker Research:

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 for the withdrawn subject or added to the existing data or database(s). Data generated for biomarker research before subject withdrawal of consent will remain part of the study results.

5.7 Study Drug

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug and Placebo

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib tablet	oral	Film-coated tablet	30 mg	AbbVie
Placebo tablet	oral	Film-coated tablet	NA	AbbVie
Dupilumab pre-filled syringe	SC	Solution for injection in pre-filled syringe	300 mg	Sanofi, Genzyme (Regeneron)
Placebo pre-filled syringe	SC	Solution for injection in pre-filled syringe	NA	AbbVie

The type and amount of kits dispensed will be managed by the Interactive Response Technology (IRT).

AbbVie will not supply drugs other than upadacitinib and dupilumab.

Storage and Disposition of Study Drug

Upadacitinib and placebo tablets must be stored at controlled room temperature (15° to 25°C/59° to 77°F).

Dupilumab and placebo pre-filled syringe must be stored refrigerated at 2°C to 8°C and protected from light, as specified on the label.

The investigational products are for investigational use only and are to be used only within the context of this study. The investigational products 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 on site as appropriate.

Upon receipt, study drugs should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via Interactive Response Technology (IRT) and encodes the appropriate study drugs to be dispensed at the subject's

corresponding study visit. Study drugs must not be dispensed without contacting the IRT system. Study drugs will only be used for the conduct of this study.

Packaging and Labeling

Upadacitinib and placebo tablets will be packaged in bottles with quantities sufficient to accommodate the study design. Each bottle will be labeled per local requirements. The labels must remain affixed to the bottles. Each kit label will contain a unique kit number.

Dupilumab and placebo pre-filled syringes will be packaged in cartons with quantities sufficient to accommodate the study design. Each pre-filled syringe and carton will be labeled as required per country requirements. Labels must remain affixed to the syringe and carton. Each kit label will contain a unique kit number.

Dispense Study Drug

The type and amount of kits dispensed will be managed by the IRT. Dupilumab and placebo pre-filled syringe will be dispensed through IRT every 2 weeks, and upadacitinib and placebo tablets will be dispensed through IRT every 4 weeks.

Upadacitinib and placebo tablets 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 baseline (Day 1) procedures are completed. At the visits specified, the site personnel will review returned study drug kits and empty study drug packaging to verify compliance.

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.

Study Drug Administration

Upadacitinib or placebo tablets will be taken orally once daily 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. If a subject should forget to take upadacitinib or placebo tablet 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. Upadacitinib and placebo tablets should be swallowed whole and should not be split, crushed, or dissolved.

Dupilumab or placebo pre-filled syringe will be administered by SC injection at study visits on Day 1 and every other week at the study visits specified in Appendix D until Week 22.

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.

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

1. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow re-introduction 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.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects will be randomized in a 1:1 ratio to one of two treatment groups:

- Treatment A: Upadacitinib 30 mg + placebo pre-filled syringe (N = 325)
- Treatment B: Dupilumab 300 mg + placebo tablets (N = 325)

Randomization will be stratified by baseline disease severity (moderate [vIGA-AD 3] vs. severe [vIGA-AD 4]) and age (< 40, ≥ 40 to 65, ≥ 65 years).

Blinding

All AbbVie personnel with direct oversight of the conduct and management of the trial, with the exception of AbbVie Drug Supply Management Team, will remain blinded to the study. All study site personnel involved in the study and the subjects will remain blinded to the 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. In addition, dupilumab pre-filled syringe and placebo pre-filled syringe will be administered to the subjects at the investigative site. Both types of pre-filled syringes will be provided in identical cartons. The cartons are sealed with tamper-evident seals. The study site personnel must not break the seals and open the cartons throughout the conduct of the study. The investigator will designate an unblinded administrator to administer the injection to the subject. The designated unblinded administrator must not have involvement with any other study-related activities.

To maintain the blind for the study, only the designated unblinded administrator will be allowed to break the tamper-evident seals of the cartons just prior to administration. If a kit of dupilumab/placebo is dispensed by IRT, it should remain sealed until the time of drug administration. If for any reason the study drug administration is not performed, the carton should remain sealed, and should be accounted and prepared for destruction without breaking the tamper evident seal, maintaining the blind of the study. Other study site personnel, including safety and efficacy evaluators, must not be involved with administration of the injectable dosage forms. To maintain the blind for the subject, appropriate measures must be taken to ensure the subjects do not see the study drug syringe or subcutaneous administration of study drug. The investigational sites must take appropriate precautions, including, but not limited to, blindfolding the subject, creating a barrier between the subject and administrator or administration site, or by any other means of blinding the subjects. The unblinded administrator will immediately discard the syringe in an appropriate container after conducting administration and prior to removing the barrier between administrator and the subject.

Empty cartons without the syringe should be retained along with the unopened cartons for accountability. If the carton with the syringe has been opened (the tamper-evident seal broken) and the

unblinded administrator is not able to administer study drug syringe for any reason, then the administrator must document the kit number and a reason(s) for not administering a specific kit. The unblinded administrator will immediately discard the syringe in an appropriate container after documenting accountability of such kit and prior to removing the barrier between administrator and the subject.

Other site personnel besides an unblinded administrator will not be made aware of the subject treatment assignments except in the event of an emergency where identification of the study drug is required for therapeutic measures. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

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

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

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.

Dupilumab and placebo pre-filled syringe dosing will be recorded on the designated eCRF. 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, and the accountability of the Study Drug/Placebo will be recorded in IRT.

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 independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

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, 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.

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 research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the exploratory research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study.

Screening and Re-Screening Procedures

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Operations Manual Section 2.1. With the exception of the QuantiFERON TB-Gold and purified protein derivative (PPD) tests (requirements outlined in Operations Manual Section 3.17, otherwise exclusionary laboratory values can be re-tested once during the Screening Period. If the re-tested laboratory value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

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

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

- HBV, HCV and HIV serology

- QuantiFERON Tuberculosis [TB] Gold or equivalent and/or a PPD test (or both if required per local guidelines)
- CXR
- Electrocardiogram (ECG)

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 Bacille Calmette-Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and travel to, reside in, or work in TB endemic locations.

Drug and Alcohol Screen

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

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.

Subjects will complete the following questionnaires (described below) as specified in Operations Manual Section 2.1: Worst Pruritus NRS; ADerm-IS; and Head and Neck - Patient Global Impression of Severity (HN-PGIS). The subject should complete the questionnaires before site personnel perform any clinical assessments and preferably before any interaction with site personnel has occurred to avoid biasing the subject's response.

A validated translation will be provided in their local language, as applicable. All PROs are collected electronically.

The PRO instrument should be completed prior to drug administration on Day 1 and prior to any discussion of adverse events 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 daily from Screening through Week 16 using an electronic hand-held device that will be given to subjects to take home at Screening. Hand-held device usage ends at the Week 16 visit (subjects should provide their response on the site's tablet at the Week 16 study visit). Starting at the Week 16 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 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 Baseline; devices will be given to subjects to take home at Screening.

Head and Neck Patient Global Impression of Severity (HN-PGIS)

The HN-PGIS asks subjects to describe the severity of their head and neck AD symptoms right now. Subjects rate their head and neck 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 HN-PGIS will be administered on the tablet at site visits throughout the study.

Investigator Assessment

The investigator assessments will be recorded on paper worksheets and entered into the eCRF and conducted at the study visits specified in Operations Manual Section 2.1. 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 assessor should evaluate the subject at each visit for the duration of the study. A back-up assessor should be identified. The 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 primary 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, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

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

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

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. It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks before first dose of study drug or administered at least 12 weeks after the last injection. If the herpes zoster vaccine is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing 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 herpes zoster vaccine should not be administered. See Prohibited Medications/Therapy for a list of commonly used live vaccines that are prohibited during study participation.

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

Tuberculosis Testing/Tuberculosis Prophylaxis

The TB screening 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 questionnaire (Operations Manual Section 3.2) and tested for TB infection by QuantiFERON-TB Gold test. The site staff will complete the TB risk questionnaire in its entirety (Part I and Part II) and enter the data into the appropriate eCRF. The TB risk questionnaire will be completed annually (Part I only) for all subjects, regardless of TB test results. One or more "yes" response on the TB risk questionnaire (Part I and Part II questions) indicates increased risk of TB.

If a subject had a negative PPD test within 90 days prior to Screening and a QuantiFERON-TB Gold test cannot be performed by the central laboratory at Screening and source documentation is available, TB testing by PPD Skin Test (also known as a TB Skin Test or Mantoux 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.

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 CXR 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 CXR. Subjects with no signs or symptoms and a CXR 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.

If an annual TB test is newly positive (seroconversion), a CXR needs to be performed as soon as possible to aid in distinguishing active versus latent TB and subsequent annual TB follow-up tests are not required. Any positive TB test after the patient 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 investigation and a repeat test before the next scheduled annual TB retest, the case (including the TB test results) should be discussed with the AbbVie TA MD.

TB test

- The QuantiFERON-TB Gold test (or equivalent) should be performed at Screening on all subjects. The PPD skin test should be utilized when the QuantiFERON-TB Gold test (or equivalent) is not possible or if both tests are required per local guidelines.
- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test and/or PPD skin test 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, both will be performed. If either PPD or QuantiFERON-TB Gold is positive, the TB test is considered positive.
- The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold 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 alone, then the subject should have their annual TB test performed with a QuantiFERON-TB Gold test.
- If the QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold 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 PPD in the past should not be re-exposed and the PPD should be considered positive.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (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 patient is considered to be negative.

- In cases where the 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 Part I and Part II questions of the TB risk questionnaire at Screening or Part I questions annually) and has no clinical suspicion of TB, the investigator may perform a local QuantiFERON-TB Gold test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive, the test is considered positive.
- An equivalent Interferon Gamma Release Assay (IGRA) (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold.

TB prophylaxis

Note: Rifampicin and Rifapentine are not allowed for 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 must be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

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 should not be withheld. Two to four 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 CXR will not be required if the subject had a previous normal CXR (posterior-anterior and lateral views) within 90 days of Screening, provided all source documentation is available at the site, as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test.

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 Screening (Operations Manual Section 2.1). 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

Biomarker Sampling

Optional biospecimens (blood, serum, plasma, and skin biopsies) will be collected for biomarker research 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. The samples may be retained while research on upadacitinib (or drugs of this class) or atopic dermatitis and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Height and Body Weight

Height and body weight will be measured without shoes at visits specified in Appendix D. 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, and body temperature will be obtained at visits 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 visits specified in Appendix D. The physical examination performed on Study Day 1 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.

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), due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

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

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

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

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

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

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

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr><td>Hematocrit
Hemoglobin
RBC count
WBC count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count</td><td rowspan="3">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="3"><u>Central Lab Tests:</u>
Estimated glomerular filtration rate (eGFR)
International normalized ratio (INR)
Serum pregnancy (beta human chorionic gonadotropin [bHCG]) test
<u>Hepatitis Screening:</u>
Hepatitis B surface antigen (HBs Ag)
Hepatitis B surface antibody (HBs Ab)
Hepatitis B core antibody (HBc Ab)
Hepatitis B virus deoxyribonucleic acid polymerase chain reaction (HBV DNA PCR [reflex only])
Hepatitis C virus antibody (HCV Ab)
Hepatitis C virus ribonucleic acid (HCV RNA [reflex only])
Human immunodeficiency virus antibody (HIV Ab)
QuantiFERON-TB Gold
High-sensitivity C-reactive protein (hsCRP)
Follicle stimulating hormone (FSH)[b]
Drug and alcohol screen
<u>Local Lab Tests:</u>
Urine pregnancy test
Varicella antibody, if indicated
PPD test/T-SPOT TB</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 only for female < 55 years old.

Pregnancy Tests (Serum and Urine)

A serum pregnancy test will be performed for female 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;
- Negative, the subject can be enrolled into the trial;

- 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 in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

A urine pregnancy test will be performed for all female of childbearing potential at the Baseline Visit prior to the first dose of study drug and at minimum at monthly intervals at study visits. More frequent pregnancy tests will be performed throughout the study if required per local requirements. If the End-of-Treatment follow up period is longer than 30 days, female subjects should perform monthly pregnancy tests at home, and the results of the monthly at home tests should be communicated to the site.

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin.
- If the baseline or post-baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started or resumed. If the serum pregnancy test is positive, study drug must be permanently discontinued. In the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later) to document continued lack of a positive result. 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 during the course of the study a female becomes surgically sterile or post-menopausal and complete documentation as described in *Contraception Recommendations* for Female 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.

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 (HBV):

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

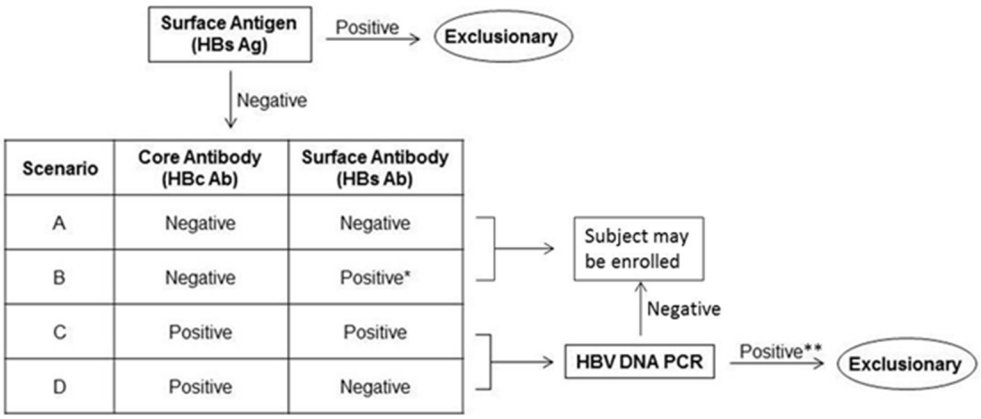
- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will trigger automatic reflex testing for 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 1, Scenarios A and B).
- For a subject who has had a 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 1, Scenario B).*
- For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab requires HBV DNA PCR testing (automatic reflex testing; Figure 1, Scenario B).
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 1, Scenarios C and D). A result for HBV DNA that exceeds detection sensitivity will be considered positive.

Figure 2. Interpretation and Management of HBV Serologic Test Results



* A positive test result for HBs Ab is expected for subjects who have had a HBV vaccination. For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab 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 every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab.

- A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.
- A subject with a negative result for HBV DNA testing may be enrolled.

- Where mandated by local requirements: A positive result for HBs Ab requires HBV DNA PCR testing.
  - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.
  - For subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening, HBV DNA PCR test should be performed every 12 weeks. HBV DNA PCR testing 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.

Hepatitis C Virus (HCV)

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

Human Immunodeficiency Virus (HIV)

Subjects with HIV infection (positive HIV test) are excluded from study participation. An anti-HIV antibody (Ab) test 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. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Discontinuation of Study Drug and Subjects Withdrawal

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 should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

Discontinuation of Study Drug and Continuation of Study Participation

Subjects may discontinue study drug treatment but may choose to continue to participate in the study. A subject who discontinues one treatment (injection or tablet) will be discontinued from the other treatment (tablet or injection). 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 should adhere to all study procedures except for annual TB testing, dispensing study drug, and blood sample collection for optional exploratory research and validation studies. Once the subject has discontinued study drug, all rescue and efficacy driven discontinuation criteria no longer apply, and subjects should be treated per standard of care. 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 (discontinuation of study drug treatment and study participation; withdrawal of informed consent) for any reason at any time. If a subject prematurely discontinues study participation, the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, an End-of-Treatment Follow-up visit or phone call may be completed 12 weeks after the last injection to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. Subjects who discontinue the study prematurely after randomization will not be replaced.

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.

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, 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 adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

If any of the following serious adverse events (SAEs) are reported, then the following supplemental report must be completed:

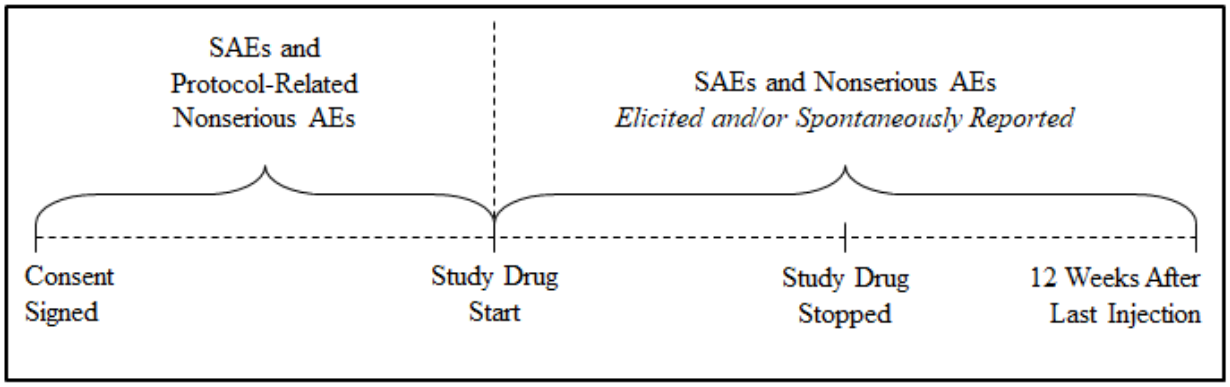
Adverse Event	Supplemental Form
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Venous thromboembolism**	Cardiovascular (Cardiac) AE eCRF Myocardial Infarction and Unstable Angina AE eCRF Heart Failure Adverse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

If an adverse event meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or Contract Research Organization (CRO) (as appropriate) as a serious adverse event within 24 hours of the site being made aware of the serious adverse event:

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 adverse events reported from the time of study drug administration until 12 weeks after the last injection will be collected, whether solicited or spontaneously reported by the subject. Subjects who discontinue study drug treatment but continue to participate in the study will have AEs collected for the remainder of study participation. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signs the study-specific informed consent.

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



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

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

Adverse Events of Special Interest

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

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

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

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

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

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

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

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

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

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 12 weeks after the last injection.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 12 weeks after the last injection. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

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

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 12 weeks after the last injection 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 adverse event 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 Events of 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 (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email FAX to:	[redacted]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Office:
Email: [redacted]

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

Primary Therapeutic Area Scientific Director:
CONTACT FOR ALL NON-EMERGENCY ISSUES:
[redacted]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Email:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT
[redacted]
AbbVie Inc.
1500 Seaport Boulevard
Redwood City, CA 94063

Contact Information:

Office: [redacted]
Mobile:
Email:

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: [redacted]	

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

6.2 Toxicity Management

The toxicity management of the AEs including AEs of special interest consists of safety monitoring (review of AEs on an ongoing basis, and periodical/ad hoc review of safety issues by a safety data monitoring committee), and, if applicable, interruption of study drug dosing with appropriate clinical

management and/or discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

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

Management of Hypersensitivity

Subjects should be closely monitored and assessed for the development of signs and symptoms of hypersensitivity reactions, including anaphylaxis. Study drug should be interrupted and appropriate therapy be instituted if a subject develops clinically significant hypersensitivity reactions.

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 Serious Gastrointestinal Events

Subjects presenting with the onset of signs or symptoms of a gastrointestinal perforation should be evaluated promptly for early diagnosis and treatment. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued from study drug.

Management of Cardiovascular Events and Embolic/Thrombotic Events

Subjects presenting with potential cardiovascular events should be appropriately assessed and carefully monitored. These events will be reviewed and adjudicated by an independent Cardiovascular Adjudication Committee (CAC) in a blinded manner.

Management of Malignancy

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

Management of 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 Fridericia's correction formula (QTcF) value > 500 msec, OR a change of QTc interval > 60 msec from baseline.

Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in, and may require a supplemental eCRF to be completed (see Protocol Section 6.1 [Complaints and Adverse Events]). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 3, the repeat testing must occur as soon as possible.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with new sample • If hemoglobin decreases ≥ 3.0 g/dL from baseline, without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, 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 if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5. A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). • Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • Interrupt study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample. • Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Screening who develop the following should have HBV DNA PCR testing performed within one week (based on initial elevated value): 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. 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 and ALT or AST elevations persist. For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).
Serum Creatinine	• If serum creatinine is > 1.5 × the Baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × Baseline value and ≤ ULN. For the above serum creatinine elevation scenario, complete the appropriate supplemental renal eCRF(s).
Creatine Phosphokinase	• If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subjects may continue study drug at the investigator's discretion. • If CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. For the above CPK elevation scenarios, complete supplemental increased CPK eCRF.

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.

The operation of the DMC data review involves data preparation by AbbVie (for blinded data) and an independent CRO (Axio Research for unblinded data to DMC), DMC review of the data at a prespecified schedule (every 4 months) or ad hoc if needed, DMC report with recommendations provided to the AbbVie Contact, and triage of the recommendations the AbbVie Contact to the appropriate parties (AbbVie Study Management Team or Internal Review Committee). The first DMC meeting is expected to occur approximately 4 months after the first subject first dose date.

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. In addition, the treatment outcomes will not be communicated from the DMC to the Study Teams.

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

6.4 Other Safety Data Collection

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

6.5 SUSAR Reporting

AbbVie will be responsible for 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 DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

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

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the final database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Intent-to-Treat (ITT) Population consists of all randomized subjects and will be used for the efficacy analyses. A Per-Protocol Population may be defined if deemed necessary to exclude subjects with protocol violations that will affect the primary endpoint. If defined, the criteria to determine 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 Per-Protocol Population, if defined, will be used to analyze the primary efficacy endpoint.

The Safety Population consists of all randomized subjects who received at least 1 dose of study drug including placebos.

7.3 Statistical Analyses for Efficacy

All efficacy endpoints will be analyzed in the ITT population to test the superiority of upadacitinib over dupilumab. In addition, the primary efficacy endpoints will be analyzed in the Per Protocol Population, if defined. Subjects will be included in the treatment group to which they are randomized.

Categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by vIGA-AD categories (vIGA-AD 3 or 4). Continuous variables will be analyzed using mixed-effect model with repeated measures (MMRM).

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

Primary Analysis

The primary endpoint is the proportion of subjects achieving EASI 75 at Week 16.

Comparison of the primary endpoint will be made between the upadacitinib group and the dupilumab group using the CMH test, stratified by vIGA-AD categories. Non-responder imputation (NRI) will be the primary approach to handle missing values, with multiple Imputation (MI) as the sensitivity approach to handle missing values. Per-protocol analysis, if defined, will be used as another sensitivity analysis.

Secondary endpoints will be analyzed in the ranked order as outlined in Section 3.3.

Sample Size Estimation

Approximately 650 subjects (18 - 75 years old) will be randomized to upadacitinib 30 mg or dupilumab in a ratio of 1:1 (325 subjects per treatment group). Assuming an EASI 75 response rate of 50% in the dupilumab arm, this sample size will provide more than 80% power to detect at least a 12% treatment difference using two-sided test at a 0.05 significant level.

7.4 Statistical Analyses for Safety

The safety analyses will be carried out using the Safety Population 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 MedDRA. Treatment-emergent AEs (TEAEs) are defined as those that began or worsened in severity after the first dose of study drug and no more than 5 half-lives of the drug after the last dose of study drug. Specifically, 30 days will be used for upadacitinib, and 84 days (12 weeks) will be used for dupilumab. 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, 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 subject with evaluations meeting criteria for pre-defined Potentially Clinically Significant values will be summarized.

7.5 Statistical Analysis of Optional Proteomic Biomarker Data

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

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

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

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 patient reported outcome design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health. Daily Worst Pruritus NRS and daily and weekly ADerm-IS ePROs will be collected from subjects electronically every evening via a hand-held device provided to the subject at Screening. Hand-held device usage stops at the Week 16 visit. The Week 16 and subsequent NRS will be completed electronically via an onsite tablet device. ADerm-IS will be collected only during the Screening period and at the Baseline Visit. The hand-held electronic device will be programmed to allow data entry once per day. The ePRO data of HN-PGIS 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.

12 REFERENCES

1. Kunz B, Oranje AP, Labrèze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology. 1997;195(1):10-9.
2. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol. 2012;26(9):1045-60.
3. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. Pediatrics. 2008;122(4):812-24.
4. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergoly and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy. 2006;61(8):969-87.
5. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-49.
6. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287-303.
7. Simpson EL, Bieber T, Guttman-Yaasky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335-48.

8. Chung-Ching C, Di Meglio P, Nestle FO. Harnessing dendritic cells in inflammatory skin diseases. Semin Immunol. 2011;23(1):28-41.
9. Nobbe S, Dziunycz P, Muhleisen B, et al. IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. Acta Derm Venereol. 2012;92(1):24-8.
10. Genovese MC, Smolen JS, Weinblatt ME, et al. Efficacy and Safety of ABT-494, a Selective JAK-1 Inhibitor, in a Phase IIb Study in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate. Arthritis Rheumatol. 2016;68(12):2857-66.
11. Kremer JM, Emery P, Camp HS, et al. A Phase IIb Study of ABT-494, a Selective JAK-1 Inhibitor, in Patients With Rheumatoid Arthritis and an Inadequate Response to Anti–Tumor Necrosis Factor Therapy. Arthritis Rheumatol. 2016;68(12):2867-77.
12. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet Online. 2018;391(10139):2513-24.
13. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Online. 2018;391(10139):2503-12.
14. AbbVie. Upadacitinib Investigator's Brochure Edition 8. 22 August 2018.
15. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116-32.
16. Dupixent [summary of product characteristics]. Paris, France: Sanofi-Aventis Groupe. 2017.
17. Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2017.
18. Banerjee S, Biehl A, Gadina M, et al. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs. 2017;77(5):521-46.
19. Norman P. Selective JAK1 inhibitor and selective Tyk2 inhibitor patents. Expert Opinion on Therapeutic Patents. 2012;22(10):1233-49.
20. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;944-47.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
AD	Atopic dermatitis
ADerm-IS	Atopic dermatitis impact scale
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AxSpA	Axial spondyloarthritis
BCG	Bacille Calmette-Guérin
BSA	Body surface area
BUN	blood urea nitrogen
CAC	Cardiovascular adjudication committee
CD	Crohn's disease
CFR	Code of Federal Regulations
CLDN1	Claudin 1
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPK	Creatine kinase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest x-ray
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI 75/90/100	75%/90%/100% reduction in Eczema Area and Severity Index

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
ePRO	Electronic patient reported outcome
EU	European Union
EudraCT	European Clinical Trials Database
FLG	Filaggrin
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBc	Anti-hepatitis B core antibodies
HBc Ab	Hepatitis B core antibodies
HBs	Anti-hepatitis B surface antibody
HBs Ab	Anti-hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C antibody
HDL-C	high-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
HLA	Human Leukocyte Antigen
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFN	interferon
IFN-□	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IGRA	Interferon-gamma release assay
IL	Interleukin

IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JAK	Janus kinase
LDL-C	low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	mixed-effect model with repeated measures
MTX	Methotrexate
NCI	National Cancer Institute
NK	Natural killer
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
NRS	Numerical rating scale
PCR	Polymerase chain reaction
PD	Premature discontinuation
PDE4	Phosphodiesterase type 4
PGIS	Patient Global Impression of Severity
PPD	Purified protein derivative
PRO	patient-reported outcome
PsA	Psoriatic arthritis
PT	Preferred term
PUVA	Psoralen and ultraviolet A
QD	Once daily
QTc	QT interval corrected
QTcF	Friedericia's correction formula
RA	Rheumatoid arthritis

RBC	red blood cell
RNA	ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SOC	System organ classes
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
Tdap	Tetanus-diphtheria-acellular pertussis
TEAE	Treatment emergent adverse event
TNF	tumor necrosis factor
TPPA	Treponema pallidum particle agglutination assay
TRUST	Toluidine Red Unheated Serum Test
Tyk2	Tyrosine kinase 2
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
UV	Ultra violet
vIGA-AD	Validated Investigator Global Assessment for atopic dermatitis
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-046: Atopic Dermatitis: Evaluation of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 17 October 2018

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Clinical Program Development
		Immunology Clinical Development
		Immunology Clinical Development
		Immunology Clinical Development
		Data and Statistical Sciences
		Pharmacovigilance & Patient Safety
		Immunology Translational Science
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the Operations Manual Section 2.1.

Study Activities Table

Activity	Screening	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Un-scheduled Visit for Rescue Treatment	PD Visit	F/U Visit (12 Wks After Last Injection)
INTERVIEWS & QUESTIONNAIRES																		
Subject information and informed consent	✓																	
Eligibility criteria	✓	✓																
Medical/surgical history	✓	✓																
Alcohol and nicotine use	✓																	
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk assessment form	✓																	
Review pregnancy avoidance recommendations (females of childbearing potential only)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PRO																		
Worst Pruritus NRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ADerm-IS	✓	✓																
HN-PGIS	✓	✓	✓	✓	✓		✓		✓		✓		✓		✓			
EXAMS and Local Labs																		
Body Weight	✓	✓			✓						✓				✓	✓	✓	
Height	✓																	
Vital Signs (at FU if needed to monitor AEs)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)
Physical Exam (at FU if needed to monitor AEs)	✓	✓			✓						✓				✓			(✓)
12-lead ECG	✓																	

Activity	Screening	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Un-scheduled Visit for Rescue Treatment	PD Visit	F/U Visit (12 Wks After Last Injection)
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator Assessment vIGA	✓	✓																
Investigator Assessment EASI, BSA	✓	✓	✓	✓	✓		✓		✓		✓		✓		✓	✓	✓	
Chest x-ray for TB assessment	✓																	
Urine pregnancy test (for all female subjects of childbearing age)		✓			✓		✓		✓		✓		✓		✓			
CENTRAL LABS																		
Serum pregnancy test (for all female subjects of childbearing age)	✓																	
hsCRP, clinical chemistry, hematology, urinalysis	✓	✓		✓	✓		✓		✓		✓		✓		✓	✓	✓	✓ (only as needed for AEs)
Drug and alcohol screen	✓																	
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)	✓																	
HIV, HBV, and HCV	✓																	
Total Serum IgE		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Whole Blood for RNA		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Whole blood (plasma for proteomic and targeted protein investigations)		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Whole blood (serum for proteomic and targeted protein investigations)		✓	✓	✓			✓				✓				✓			

Activity	Screening	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Un-scheduled Visit for Rescue Treatment	PD Visit	F/U Visit (12 Wks After Last Injection)
Optional Biomarker: Whole blood for DNA		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Lesional/nonlesional skin biopsies		✓		✓							✓							
℞ TREATMENT																		
Randomization/drug assignment		✓																
Administration of Injectable study drug/placebo; retain unused carton sealed or empty carton without syringe.		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Dispense study drug		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Perform blinded drug accountability and reconciliation, retain unused carton sealed or empty carton without syringe (instruction for retaining cartons is not relevant to Week 24, Un-scheduled Visit, or PD Visit).				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

APPENDIX E. OPERATIONS MANUAL

abbvie

Operations Manual for Clinical Study Protocol M16-046

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

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

FULL TITLE: A Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

1 CONTACTS

Sponsor/ Emergency Medical Contact	**Sponsor contact for all non-emergency issues:** [redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064 **Sponsor emergency contact:** [redacted] 1500 Seaport Boulevard Redwood City, CA 94063 [redacted] **Number:**
Safety Concerns	Immunology Safety Team [redacted] 1 North Waukegan Road North Chicago, IL 60064
SAE Reporting outside of RAVE	Email: [redacted]
Protocol Deviations	[redacted] AbbVie Inc. 41-45 Marinou Antypa Street 141 21 N. Irakleio Athens, Greece
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214
Biomarker Sample Storage	BioStorage Technologies Inc 2910 Fortune Circle West, Suite E Indianapolis, IN 46241

abbvie

TABLE OF CONTENTS

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. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

Activities are grouped by category: Interviews and Questionnaires, Patient Reported Outcomes (PRO), Exam, Local Lab, Central Lab, and Treatment. Further information about each activity is provided in Section 5.10 of the protocol.

SCREENING:

INTERVIEWS & QUESTIONNAIRES	• Subject Information and Informed consent[a] • Eligibility criteria • Medical/surgical history	• Alcohol and nicotine use • Prior/concomitant therapy • Latent Tuberculosis (TB) risk factor questionnaire
PRO	• Worst Pruritus Numerical Rating Scale (NRS) • Atopic Dermatitis Impact Scale (ADerm-IS)	• Head and Neck Patient Global Impression of Severity (HN-PGIS) • Dispense subject hand-held device
EXAM	• Body weight • Height • Vital signs • Physical examination • 12-lead Electrocardiogram (ECG)[b] • Adverse event (AE) assessment[c]	• Investigator Assessments: Eczema Area and Severity Index (EASI), body surface area (BSA), validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) • Chest x-ray for TB assessment
CENTRAL LAB	• Serum pregnancy test (for all female subjects of childbearing potential)[f] • Follicle stimulating hormone (FSH)[g] • High sensitivity C-reactive protein (hsCRP) • Clinical Chemistry • Hematology • Urinalysis • Drug and alcohol screen	• TB Test (QuantiFERON TB Gold test [or interferon gamma release assay (IGRA) equivalent such as T-SPOT test] and/or local purified protein derivative [PPD] skin test, if required)[d] • Human immunodeficiency virus (HIV),[e] hepatitis B (HBV), and hepatitis C (HCV) Screening

a. Obtain informed consent prior to performing any study-related procedures.
b. The ECG obtained at Screening will serve as the Baseline reference. Screening ECG not required if subject had normal ECG within 90 days of Screening (refer to Section 5.10 of the protocol for additional details).
c. Only serious adverse events (SAEs) and protocol-related nonserious AEs collected at Screening (refer to Section 6 of the protocol for additional details).
d. The QuantiFERON-TB Gold test (or equivalent) should be performed on all subjects. The PPD skin test should be utilized when the QuantiFERON-TB Gold test (or equivalent) is not possible or if both tests are required per local guidelines.
e. Anti-HIV antibody (Ab) performed at Screening, unless prohibited by local regulations (refer to Section 5.10 of the protocol for additional details).
f. For all females of childbearing potential (refer to Section 5.10 of the protocol for additional details).

g. FSH tested at Screening if female subject is ≤ 55 years of age AND has had no menses ≥ 12 months AND has no history of permanent surgical sterilization (refer to Section 5.10 of the protocol for additional details).

BASELINE/DAY 1:

INTERVIEWS & QUESTIONNAIRES	• Eligibility criteria • Medical/surgical history • Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS • ADerm-IS	• HN-PGIS • Subject hand-held device review
EXAM	• Body weight • Vital signs • Physical exam	• AE assessment • Investigator Assessments (EASI, BSA, vIGA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total immunoglobulin E (IgE) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA • Optional Biomarker: Lesional/nonlesional skin biopsies
TREATMENT	• Randomization/drug assignment • Dispense study drug	• Administration of injectable study drug/placebo • Retain unused carton sealed, or empty carton without the syringe

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

WEEK 1:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
CENTRAL LAB	• Total IgE • Optional Biomarker: Whole blood RNA • Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum)	• Optional Biomarker: Whole blood DNA

WEEK 2:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
CENTRAL LAB	• Total IgE • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA • Optional Biomarker: Lesional/nonlesional skin biopsies
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 4:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS • HN-PGIS	• Subject hand-held device review
EXAM	• Body weight • Vital signs • AE assessment	• Physical exam • Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 6:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• Subject hand-held device review
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 8:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total IgE (serum) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 10:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• Subject hand-held device review
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 12:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 14:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• Subject hand-held device review
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 16:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device return and review
EXAM	• Body weight • Vital signs • AE assessment	• Physical exam • Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total IgE (serum) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA • Optional Biomarker: Lesional/nonlesional skin biopsies
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 18:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 20:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 22:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 24:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS
EXAM	• Body weight • Vital signs • AE assessment	• Physical exam • Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total IgE (serum) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA
TREATMENT	• Perform blinded drug accountability and reconciliation	

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	
EXAM	• Body weight • Vital signs	• AE assessment • Investigator Assessments (EASI and BSA)
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Perform blinded drug accountability and reconciliation	

PREMATURE D/C VISIT:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	
EXAM	• Body weight • Vital signs	• AE assessment • Investigator Assessments (EASI and BSA)
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Perform blinded drug accountability and reconciliation	

F/U VISIT (12 Weeks After Last Injection):

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy
EXAM	• AE assessment
CENTRAL LAB	• hsCRP • Clinical Chemistry • Hematology • Urinalysis

Notes: A Follow-Up Visit will occur approximately 12 weeks after the last injection to obtain additional safety information. If the follow up period is longer than 30 days, female subjects should perform monthly pregnancy tests at home, and the results of the monthly at home tests should be communicated to the site. For subjects who prematurely discontinued study participation and are willing to provide additional information, this visit may be a telephone call if a site visit is not possible. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation with completion of at least one study visit occurring at least 12 weeks after the last injection.

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

3 APPENDICES

3.1 STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
AD	Atopic dermatitis
ADerm-IS	Atopic dermatitis impact scale
AE	Adverse event
BSA	Body surface area
DNA	Deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EU	European Union
FSH	Follicle-stimulating hormone
F/U	Follow-up
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HN-PGIS	HN-PGIS
hsCRP	High-sensitivity C reactive protein
IGRA	Interferon gamma release assay
IgE	Immunoglobulin E
NRS	Numerical rating scale
PPD	Purified protein derivative
PRO	Patient reported outcome
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
TB	Tuberculosis
vIGA-AD	Validated Investigator Global Assessment for atopic dermatitis

3.2 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

3.3 WORST 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

abbvie

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

Instructions: The following questions are about your atopic dermatitis (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 atopic dermatitis (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 0 1 2 3 4 5 6 7 8 9 10 Extremely limited ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
7.	During the past seven days, how **difficult** was it for you **to concentrate** due to AD?	Not difficult 0 1 2 3 4 5 6 7 8 9 10 Extremely difficult ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8.	During the past seven days, how **self-conscious** did you feel due to AD?	Not self-conscious 0 1 2 3 4 5 6 7 8 9 10 Extremely self-conscious ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
9.	During the past seven days, how **embarrassed** did you feel due to AD?	Not embarrassed 0 1 2 3 4 5 6 7 8 9 10 Extremely embarrassed ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
10.	During the past seven days, how **sad** did you feel due to AD?	Not sad 0 1 2 3 4 5 6 7 8 9 10 Extremely sad ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

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

3.5 HEAD AND NECK - PATIENT GLOBAL IMPRESSION OF SEVERITY (HN-PGIS) QUESTIONNAIRE EXAMPLE

HEAD AND NECK - PATIENT GLOBAL IMPRESSION OF SEVERITY (HN-PGIS)

Seven point response scale

Please mark an "X" in the box (☒) that best describes the severity of your atopic dermatitis (AD) symptoms right now for **only your head and neck**.

5. Right now, my atopic dermatitis (AD) symptoms for my **head and neck** 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.

3.6 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.

3.7 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.

Document Approval

Study M16046 - A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis - Operations Manual for Protocol Version 1-0 - 17Oct2018

Version: 2.0 **Date:** 17-Oct-2018 08:36:00 PM **Company ID:** 10172018-00F9F683F1DDFC-00002-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	17-Oct-2018 05:25:12 PM	Author
	17-Oct-2018 05:27:46 PM	Approver
	17-Oct-2018 05:29:02 PM	Approver
	17-Oct-2018 05:35:12 PM	Approver
	17-Oct-2018 05:40:48 PM	Approver
	17-Oct-2018 06:28:43 PM	Approver
	17-Oct-2018 07:05:49 PM	Approver
	17-Oct-2018 08:35:59 PM	Approver

Document Approval

Study M16046 - A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis - Protocol Version 1-0 - EudraCT 2018-002264-57 - 17Oct2018

Version: 2.0 **Date:** 17-Oct-2018 08:36:03 PM **Company ID:** 10172018-00F9F683F1DDFD-00002-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	17-Oct-2018 05:25:12 PM	Author
	17-Oct-2018 05:27:46 PM	Approver
	17-Oct-2018 05:29:02 PM	Approver
	17-Oct-2018 05:35:12 PM	Approver
	17-Oct-2018 05:40:48 PM	Approver
	17-Oct-2018 06:28:43 PM	Approver
	17-Oct-2018 07:05:49 PM	Approver
	17-Oct-2018 08:35:59 PM	Approver

abbvie

Protocol for Study M16-046 – Heads Up

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

VERSION:	2.0	DATE:	13 March 2020
SPONSOR:	For Non-EU Countries:* AbbVie Inc. For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie)	NUMBER OF SITES:	Up to 160
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EUDRACT:	2018-002264-57

FULL TITLE: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

Sponsor contact for all non-emergency issues:

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

Office: [redacted]
Mobile:
Email:

Sponsor emergency contact:

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

Office:
Mobile:
Email:

[redacted]

EMERGENCY 24-hour Number: [redacted]

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

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Protocol	Date
Version 1.0	17 October 2018
Version 1.1 (VHP Countries: Czech Republic, Denmark, Finland, Germany, Hungary, Italy, Norway, Poland, Spain, Sweden, United Kingdom)	18 February 2019
Version 1.2 (Ireland only)	18 February 2019
Administrative Change 1	31 May 2019
Version 1.3 (United States only)	25 June 2019

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

Summary of Protocol Changes:

- Section 2.2, Benefits and Risks to Subjects:
  - Added text describing other treatments and AEs associated with them.
  - Added that events of deep vein thrombosis and pulmonary embolism have been reported in
  - patients receiving JAK inhibitors including upadacitinib.
  - A statement was added about the risk of NMSC and other malignancies observed in the Phase 3 RA studies with use of upadacitinib.

  Rationale: Statements are applicable to the overall benefit-risk profile of upadacitinib and consistent with the latest version of the upadacitinib Investigator's Brochure.
- Section 3.3, Secondary Endpoints
  - Clarified the wordings to the secondary endpoints:
    2. Proportion of subjects achieving a 100% reduction in EASI (EASI 100) from Baseline at Week 16
    3. Proportion of subjects achieving a 90% reduction in EASI (EASI 90) from Baseline at Week 16

  Rationale: To align with the wording of the primary endpoint.
- Section 3.3, Secondary Endpoints
  - Added the following ranked secondary endpoints:
    4. Percent change from Baseline to Week 4 in Worst Pruritus NRS
    5. Proportion of subjects achieving a 75% reduction in EASI (EASI 75) from Baseline at Week 2
    6. Percent change from Baseline to Week 1 in Worst Pruritus NRS

Rationale: To align with endpoints used in other AD trials.

- Section 3.4, Additional Endpoints
  - Clarified the wording to the worst pruritus endpoint:
    - Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline for subjects with Worst Pruritus NRS ≥ 4 at Baseline

  Rationale: To align with endpoints used in other AD trials.
- Section 4.1, Overall Study Design and Plan
  - Added the following statement: "Subjects who complete Study M16-046 will have the option to enroll into an open-label study of oral upadacitinib 30 mg QD in which they will be treated for an additional 52 weeks."
  - Also, clarified the End-of-Treatment Follow-up Visit statement to the following: "The End-of-Treatment Follow-up Visit will be 12 weeks after the last injection for subjects who do not enroll into the open-label study."

  Rationale: Provides an option for subjects who complete this study to enroll into an open-label study of upadacitinib.
- Section 5.1 Eligibility Criterion #8: Text was changed from "Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit …" to "Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit …" and "(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 #9: Regarding continued use of birth control after study participation, "after the last dose of study drug" was corrected to read "after the last injection."

  Rationale: Updated to account for the longer half-life of dupilumab compared to upadacitinib.
- Section 5.1 Eligibility Criterion #14: Updated the Criterion number stated for 'Topical treatments (with the exception of topical emollient treatments, described in Eligibility Criterion 8), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days' to 'Criterion 6.'

  Rationale: Corrected to the correct Criterion number.
- Section 5.1 Eligibility Criterion #15: The time period after study participation until a subject may receive a live vaccination was changed from "at least 4 weeks after the last dose of study drug" to "at least 12 weeks after the last injection" to align with the washout period for dupilumab for concomitant treatments and for consistency with other Phase 3 protocols and to designate the last injection as the starting point for the 12-week time period instead of the last dose of study drug.

  Rationale: Updated to account for the longer half-life of dupilumab compared to upadacitinib.
- Section 5.1 Eligibility Criteria, Eligibility Criterion 15; and Section 5.3 Prohibited Medications and Therapy, Vaccines: Revised language regarding live vaccines to account for local requirements.

  Rationale: Countries may require longer durations between receipt of any live vaccination and first or last dose of study drug than durations stated in this protocol.

- Section 5.1 Eligibility Criterion #19: Updated herpes zoster language.

  Rationale: Updated to reflect the most current language in upadacitinib studies.

- Section 5.1 Eligibility Criterion #20: The original sentence "Subject must have no current or past history of infection including:" was corrected. It now reads: "Subject must have no current or past history of the following medical conditions:". For history of cardiovascular conditions, a statement was added that a subject must not have moderate to severe congestive heart failure (New York Heart Association Class III or IV). In addition, "uncontrolled hypertension" was deleted from the statement about blood pressure.

  Rationale: Correction of an error to clarify the eligibility criterion refers to medical conditions, not infections. Updated eligibility criterion regarding cardiovascular conditions per request of VHP.

- Section 5.1 Eligibility Criterion #20: 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:

  - 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 5.3 Prohibited Medications and Therapy, Vaccines: A correction was made to the subsection for Vaccinations to state that "vaccinations must be completed (per local) at least 4 weeks (or longer if locally required) before first dose of study drug." The previous wording was "at least 14 days."

  Rationale: Updated for consistency throughout the document.

- Section 5.3 Prohibited Medications and Therapies, Strong CYP3A Inhibitors or Inducers: Added cobicistat and troleandomycin as strong CYP3A inhibitors and rifampicin and rifapentine as strong CYP3A inducers.

  Rationale: Added cobicistat, troleandomycin, and rifapentine for consistency with examples of commonly used strong CYP3A inhibitors and inducers listed in other upadacitinib protocols; also added rifapentine and rifampicin for consistency with existing language in Section 5.10 that rifampicin and rifapentine are prohibited for concomitant use with study drug.

- 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.

- Section 5.5, Withdrawal of Subjects and Discontinuation of Study
  - Clarified the criteria regarding abnormal laboratory results.

  Rationale: Updated for consistency across protocols for the upadacitinib clinical program.
- 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 5.10 Other Study Procedures, subsection of Screening and Re-Screening Procedures, a cross reference to the Operations Manual was changed to "Tuberculosis Testing/Tuberculosis Prophylaxis below,"

  Rationale: Information was moved from the Operations Manual.
- Section 5.10 Other Study Procedures, subsection of Patient-Reported Outcomes, Section 9, Electronic Patient Reported Data, and in Appendix D the Oral vs Injectable Questionnaire (only for the United States) was added as a PRO assessment at Week 24, which measures subject preferences for route of administration (oral vs injectable) for medication for AD.

  Rationale: Addition of a PRO to evaluate subject preference for route of administration.
- Section 5.10 Other Study Procedures, subsection of Patient-Reported Outcomes, "For the Worst Pruritus NRS, ADerm-IS, and HN-PGIS," was added prior to the following text "the PRO instrument should be completed prior to drug administration on Day 1." And the text of "All PRO instruments should be completed" was added to "prior to any discussion of adverse events or any review of laboratory findings."

  Rationale: To clarify the timing of PRO instrument completion for most accurate results.
- Section 5.10 Other Study Procedures, subsection Worst Pruritus Numerical Rating Scale (NRS): A statement was added about validation of the assessment.

  Rationale: To provide information that the measure is in the process of being validated.
- Section 5.10 Other Study Procedures, subsection Tuberculosis Testing/Tuberculosis Prophylaxis, the TB risk questionnaire does not have specific sections called "Part I" and "Part II," thus their mention as part of this assessment has been removed.

Rationale: To update the language in the protocol to reflect the most recent TB risk questionnaire.

- Section 5.10 Other Study Procedures, subsection for Vital Signs: A statement was added, "For additional guidance on conventional office blood pressure measurements, please refer to the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines," and a reference to the guidelines was added.

  Rationale: Guidance reference provided on administration of conventional office blood pressure measurements provided per request of VHP.

- Section 5.10 Other Study Procedures, subsection for Pregnancy Tests (Serum and Urine):
  - Wording about pregnancy test at Screening was changed from "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 in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results" to "Still borderline ≥ 3 days later, the subject is considered a screen failure."
  - Statement about baseline or post-baseline pregnancy test changed from "In the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later) to document continued lack of a positive result" to "In the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later) to document a negative result."
  - "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." was changed to "Still borderline ≥ 3 days later, the subject must be discontinued."

  Rationale: Interpretation of pregnancy test results amended at the request of VHP.

- Section 5.10 Other Study Procedures, subsection for Hepatitis Screen: Cross references to "Figure 1" were corrected to "Figure 2."

  Rationale: Incorrect references were updated.

- 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, Pregnancy
  - Removed text regarding pregnancy in the partner of a study subject.

  Rationale: To align with language in the pivotal upadacitinib studies.

- Section 6.1, Complaints and Adverse Events, Table 4 Supplemental Electronic Case Report Forms.
  - 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.
- Section 6.2 Toxicity Management
  - Added management of herpes zoster.
  - Revised subsection for management of cardiovascular events and embolic/thrombotic events and made it specific to thrombosis events.
  - Added recommendation for periodic skin examination for patients who are at increased risk for skin cancer.

  Rationale: To align with toxicity management guidance stated in the upadacitinib Investigator's Brochure and to keep language specific to guidance above what is expected as standard of care.
- 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, Table 5 Specific Toxicity Management Guidelines for Abnormal Laboratory Values, AST or ALT parameter column.
  - Added 'increase from baseline' for the eosinophilia parameter. Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from baseline).
  - Clarified toxicity management criteria related to ALT and AST.
  - Added abbreviations to the bottom of the table.

  Rationale: Clarification.
- Section 7.3 Statistical Analysis for Efficacy, subsection for Sample Size Estimation: A rationale and reference were added for the assumption of dupilumab response rate for EASI 75 and 12% treatment difference between dupilumab and upadacitinib treatment at Week 16 of treatment.

  Rationale: Additional information provided to clarify statistical assumptions.
- Throughout document, added International Nonproprietary Name for PF-04965842.

  Rationale: Added for transparency as compound now has an International Nonproprietary Name.

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

- Updated the Sponsor emergency contact.
- Minor text edits as needed for consistency and clarity.
- Added abbreviations under Table 3.
- In the References list, 4 publications were added and 1 was deleted.
- Updated list of protocol signatures.

Summary of Operations Manual Changes

- Section 1, Contacts, updated the Sponsor emergency contact.

  Rationale: Updated personnel.

- Section 2.1, Week 2, deleted duplicate item of "Optional Biomarker: Whole blood RNA"

  Rationale: Correction of typographical error.

- Section 2.1, Week 24, PRO: Added the Oral vs Injectable Questionnaire which measures subject preferences for route of administration (oral vs injectable) for medication for AD. Also, added Appendix 3.8 for the Oral vs Injectable Questionnaire (United States only).

  Rationale: Addition of a PRO, to evaluate subject preference for route of administration.

- Section 2.1, F/U Visit (12 Weeks After Last Injection): Second note now mentions that vital signs and physical examination will also be done at F/U if needed to continue monitoring of relevant AEs (along with clinical laboratory collections).

  Rationale: Clarification of clinical process information at study visits.

abbvie

Protocol for Study M16-046 – Heads Up

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

VERSION:	3.0	DATE:	28 October 2020
SPONSOR:	For Non-EU Countries:* AbbVie Inc. For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie)	NUMBER OF SITES:	Up to 160
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EUDRACT:	2018-002264-57

FULL TITLE: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

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

Office: [redacted]
Mobile:
Email:

EMERGENCY 24-hour Number: [redacted]

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

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Protocol	Date
Version 1.0	17 October 2018
Version 1.1 (VHP Countries: Czech Republic, Denmark, Finland, Germany, Hungary, Italy, Norway, Poland, Spain, Sweden, United Kingdom)	18 February 2019
Version 1.2 (Ireland only)	18 February 2019
Administrative Change 1	31 May 2019
Version 1.3 (United States only)	25 June 2019
Version 2.0	13 March 2020
Version 2.1 (Ireland only)	13 March 2020
Version 2.2 (VHP countries)	31 July 2020

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

Summary of Protocol Changes:

- Title Page and Section 6.1 Complaints and Adverse Events
  - Updated Sponsor contact

  Rationale: Updated personnel
- Section 3.3 Secondary Endpoints and Section 3.4 Additional Endpoints
  - The 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 has been changed from an additional endpoint to a secondary endpoint.
  - The proportion of subjects achieving an improvement (reduction) in Daily Worst Pruritus NRS ≥ 4 from Baseline for subjects with Daily Worst Pruritus NRS ≥ 4 at Baseline by day up to Day 28 has been added as an additional endpoint.

  Rationale: To escalate a currently specified additional endpoint to a key secondary endpoint (multiplicity-controlled) and add a new additional endpoint for consistency with other upadacitinib studies in AD.
- Section 7.3 Statistical Analyses for Efficacy
  - Specified that missing values due to COVID-19 will be handled by NRI-C, which will be the primary approach to handle missing values.

  Rationale: To modify statistical analysis due to the COVID-19 pandemic.

Summary of Operations Manual Changes:

- Section 1 Contacts

- Updated Sponsor contact

Rationale: Updated personnel.

abbvie

Protocol for Study M16-046 – Heads Up

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

VERSION:	4.0	DATE:	10 November 2020
SPONSOR:	For Non-EU Countries:* AbbVie Inc. For EU Countries:* AbbVie Deutschland GmbH & Co. KG (AbbVie)	NUMBER OF SITES:	Up to 160
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EUDRACT:	2018-002264-57

FULL TITLE: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

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

Office:
Mobile:
Email:
[redacted]

EMERGENCY 24-hour Number [redacted]

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

abbvie

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in 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. AbbVie is developing a small molecule inhibitor of JAK, upadacitinib, that may address the current needs for subjects with AD. The second generation of JAK inhibitors, with different selectivity profiles against JAK1, JAK2, JAK3, and Tyrosine kinase 2 (Tyk2), is in development. Upadacitinib (ABT-494) is a novel selective JAK1 inhibitor being developed for rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), axial spondyloarthritis (AxSpA), Giant Cell Arteritis, 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 over available therapies. Results from the Phase 2 study in AD showed that upadacitinib doses of 15 mg and 30 mg per day had an efficacy and safety profile that can benefit patients with moderate to severe AD.
Objective(s) and Endpoint(s):	The objective of this study is to evaluate the efficacy and safety of upadacitinib versus dupilumab for the treatment of adult subjects with moderate to severe AD who are candidates for systemic therapy. The primary endpoint is the proportion of subjects achieving a 75% reduction in Eczema Area and Severity Index (EASI 75) at Week 16.
Investigator(s):	Multicenter; investigator information on file at AbbVie.
Study Site(s):	Up to 160 sites globally
Study Population and Number of Subjects to be Enrolled:	Approximately 650 adults subjects with moderate to severe AD who are candidates for systemic therapy.
Investigational Plan:	This is a Phase 3b, randomized, double-blind, double-dummy, active comparator-controlled multicenter study.
Key Eligibility Criteria:	Demographics • Subject must be ≥ 18 years old and ≤ 75 years old AD Disease Activity • Subject has chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria during screening and baseline; • Subject meets all of the following disease activity criteria: • EASI score ≥ 16 at the Screening and Baseline Visits;

	• Validated Investigator Global Assessment for atopic dermatitis (vIGA-AD) score ≥ 3 at the Screening and Baseline Visits; • ≥ 10% body surface area (BSA) 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. • Subject has a documented history (within 6 months of the Baseline Visit) of inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) • OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, • OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks). Prior/Concomitant Therapy • No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, abrocitinib [PF-04965842], and filgotinib). • No prior exposure to dupilumab. • Subjects must not have used the following AD treatments within the timeframe specified below 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 Section 5.3) 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), 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 ratio to receive an active agent (upadacitinib or dupilumab) and the placebo of the other agent until the Week 24 visit: • Upadacitinib 30 mg tablets + placebo pre-filled syringe; OR • Dupilumab 300 mg + placebo tablet
Date of Protocol Synopsis:	10 November 2020

2 INTRODUCTION

2.1 Background and Rationale

Why This Study Is Being Conducted

Atopic dermatitis (AD) is an inflammatory, pruritic, chronic or chronically relapsing skin disease. The adult phase of AD begins at puberty and frequently continues into adulthood. In adults, disease typically involves flexural folds, face, neck, upper arms and back, and dorsal surfaces of the hands and feet.[1,2]

Management of AD primarily consists of trigger avoidance, careful attention to skin care, and both pharmacologic and nonpharmacologic treatment.[3] The 2006 PRACTALL Consensus Report recommends treatment by addition of agents in a stepwise fashion based on disease severity, starting with topical corticosteroids of increasing potency and/or a topical calcineurin inhibitor and escalating to systemic therapy for recalcitrant, severe disease.[4] Systemic immunomodulatory agents used to treat AD include cyclosporin A, azathioprine, methotrexate (MTX), mycophenolate mofetil, interferon gamma, systemic corticosteroids, and dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling.[5-7] Despite these systemic therapies, an unmet need continues to exist for patients who are non-responders or partial responders to these agents.

The Janus kinases or JAKs are a family of intracellular tyrosine kinases that function as dimers in the signaling process of many cytokine receptors. The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases. Targeting the JAK signaling pathway for AD is supported by the involvement of various pro-inflammatory cytokines that signal via JAK pathways in the pathogenesis of AD. The activation of JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to AD and other inflammatory disorders.[8,9]

Upadacitinib is an oral, reversible JAK1 selective inhibitor. JAK1 inhibition blocks the signaling of many important pro-inflammatory cytokines, including IL-2, IL-6, IL-7, and IL-15, which are known contributors to inflammatory disorders. Through modulation of these proinflammatory cytokine pathways, upadacitinib offers the potential for effective treatment of inflammatory and autoimmune disorders such as AD, rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), axial spondyloarthritis (AxSpA), and Giant Cell Arteritis. In the upadacitinib Phase 2 AD study, a statistically significant difference in the mean percent change from Baseline in Eczema Area and Severity Index (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 events (AEs), serious adverse events (SAEs), severe AEs, and AEs leading to discontinuation were similar across treatment groups. There were no deaths reported during Period 1.

Additionally, upadacitinib was studied in rheumatoid arthritis with the results of two Phase 2 studies and two Phase 3 studies available as peer-reviewed manuscripts.[10-13] Results from the Phase 2 study in AD showed that upadacitinib doses of 15 mg and 30 mg per day had an efficacy and safety profile that can benefit patients with moderate to severe AD.

Clinical Hypothesis

Based on the differentiated selectivity profile for JAK1 inhibition, upadacitinib could demonstrate an improved benefit-risk profile compared to other therapeutic strategies for patients with inflammatory diseases.

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

Additional information regarding indications under study can be found in the current edition of the upadacitinib Investigator's Brochure.[14]

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. The most common adverse events (AEs) of topical corticosteroids occur when used as monotherapy for prolonged periods and include skin thinning, acne, pigmentation, and striae. Common AEs associated with use of topical calcineurin inhibitors are transient warmth, burning, itching, or stinging at the application site.[2,15] When topical therapies are insufficient for treating the signs and symptoms of AD, systemic therapy or phototherapy are generally added to topical agents.[2,15]

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.[5,16] These guidelines recognize that insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication. 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.[5,16]

More recently, dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling, was approved for the treatment of moderate to severe AD in adults in the European Union (EU)[17] and United States (US)[18] in 2017. 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 topical corticosteroids [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.[6,7] Nearly 50% of dupilumab subjects who were IGA 0 or 1 responders at Week 16 became nonresponders by Week 52.[17] Dupilumab is generally well-tolerated, and the most common AEs are injection site reaction, conjunctivitis, and blepharitis.[5,16]

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.[5,16] Thus, there is a high unmet need for a significant number of patients with an inadequate response to currently available agents. While not approved for AD, other systemic treatments may also be utilized including methotrexate, mycophenolate mofetil, and azathioprine.[5,16]

These systemic agents all have immunomodulating properties leading to potential AEs. The most common AEs associated with use of cyclosporin are abnormal renal function tests (e.g., increased creatinine or proteinuria), hyperlipidemia, hypertension, headache, and hypertrichosis.[5,16] The most common AEs associated with methotrexate use are gastrointestinal disorders (e.g., stomatitis, oral ulcers, dyspepsia, abdominal pain, nausea, diarrhea) and abnormal liver function tests (e.g., increased aspartate transaminase [AST] or increased alanine transaminase [ALT]).[5,16] The most common AEs associated with use of mycophenolate mofetil and azathioprine are gastrointestinal disorders (e.g., nausea, vomiting, abdominal pain, cramping, bloating, anorexia) and occasional leukopenia, anemia, and thrombocytopenia.[5,16]

Taken together, these agents may generally increase the risk of infections and cytopenias, gastrointestinal disorders, and may impact renal and/or liver function.[5,16] Rarely, lymphoproliferative disorders, lymphoma, and other malignancies are associated with these agents.[5,16] Thus, there is a high unmet need for a significant number of patients with an inadequate response to currently available agents.

Upadacitinib is a novel selective orally available JAK1 inhibitor with the potential to decrease Th2 mediated skin inflammation and itch while having minimal inhibitory effects on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.[19,20]

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

Adverse events such as infections, herpes zoster reactivation, malignancies, and hematologic AEs have been observed with JAK inhibition. Events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. Malignancies have been reported in the RA clinical studies for upadacitinib. Based on the integrated data from the Phase 3 RA studies, there were comparable incidence rates of malignancies other than non-melanoma skin cancer (NMSC) between the upadacitinib 15 mg QD and 30 mg QD groups with long-term treatment. NMSC is a common malignancy in the general population. Although the incidence rate of NMSC was higher in the upadacitinib 30 mg group compared to the upadacitinib 15 mg group in the integrated analysis data, the risk of patients experiencing a NMSC when receiving upadacitinib 15 mg and 30 mg in the Phase 3 RA studies did not appear to increase over time. Based on review of the data available, no pattern of the types of malignancies was noted, the malignancies are expected for a population of patients with moderately to severely active RA, and the standardized incidence rate is within the expected range for the general population. The safety profile specific to upadacitinib is evolving, with safety results to date consistent with those known to be associated with JAK inhibition, with non-serious infections (e.g., upper respiratory tract infection or nasopharyngitis) being the most commonly reported AEs. In addition, laboratory changes observed with upadacitinib include elevations of serum transaminases, lipids, creatinine, and creatine phosphokinase; both increased and reduced hemoglobin, depending on Baseline inflammatory burden; and reductions in white blood cell counts, including natural killer (NK) cells.

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

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.[14]

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

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to evaluate the efficacy and safety of upadacitinib versus dupilumab for the treatment of adult subjects with moderate to severe atopic dermatitis who are candidates for systemic therapy.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving a 75% reduction in EASI (EASI 75) from Baseline at Week 16.

3.3 Secondary Endpoints

Ranked Secondary Endpoints:

1. Percent change from Baseline to Week 16 in Worst Pruritus Numerical rating scale (NRS)
2. Proportion of subjects achieving a 100% reduction in EASI (EASI 100) from Baseline at Week 16
3. Proportion of subjects achieving a 90% reduction in EASI (EASI 90) from Baseline at Week 16
4. Percent change from Baseline to Week 4 in Worst Pruritus NRS
5. Proportion of subjects achieving a 75% reduction in EASI (EASI 75) from Baseline at Week 2
6. Percent change from Baseline to Week 1 in Worst Pruritus NRS
7. 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

3.4 Additional Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all visits other than those listed above. In addition, the following variables will be analyzed at all visits:

- Proportion of subjects achieving a 75% reduction in EASI in the head and neck body region from Baseline
- Proportion of subjects achieving a 75% reduction in EASI in each body region (other than head and neck) from Baseline
- Proportion of subjects achieving an improvement (reduction) in Daily Worst Pruritus NRS ≥ 4 from Baseline for subjects with Daily Worst Pruritus NRS ≥ 4 at Baseline by day up to Day 28

3.5 Safety Endpoints

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

3.6 Biomarker Samples

Optional biospecimens (e.g., blood, serum, plasma, and skin biopsies) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. This research may be exploratory in nature and the results may not be included with the clinical study report.

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 with pharmacokinetics (drug metabolizing enzymes, drug transport proteins), genes within the target pathway (JAK, Tyk2, TNF), or other genes believed to be related to AD and other inflammatory diseases (Filaggrin [FLG], Claudin 1 [CLDN1], Human Leukocyte Antigen [HLA]). Research may also include epigenetic changes in DNA that may associate with the subject's response to treatment or disease. Samples for RNA and proteomics will be used to research if any genetic variants result in changes to gene expression or protein concentrations. For any samples collected in Germany, the research will be restricted to upadacitinib and AD.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b, randomized, double-blind, double-dummy, active comparator-controlled multicenter study that will evaluate the safety and efficacy of upadacitinib versus dupilumab in 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 within 6 months prior to the Baseline Visit or for whom topical treatments are otherwise medically inadvisable.

The study is comprised of a 35-day Screening Period, a 24-week double-blind treatment period, and an End-of-Treatment Follow-up Visit. Subjects who complete Study M16-046 will have the option to enroll into an open-label study of oral upadacitinib 30 mg QD in which they will be treated for an additional 52 weeks. The End-of-Treatment Follow-up Visit will be 12 weeks after the last injection for subjects who do not enroll into the open-label study.

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to one of the two arms as shown below:

- Treatment A (N = 325): Daily oral doses of upadacitinib 30 mg from the Baseline visit until the Week 24 visit, and placebo pre-filled syringe administered at the baseline visit (2 subcutaneous [SC] injections), followed by placebo pre-filled syringe (1 injection) every other week until the Week 22 visit.
- Treatment B (N = 325): Dupilumab 600 mg (2 × 300 mg dupilumab SC injection) administered at the Baseline visit, followed by dupilumab 300 mg SC injection every other week until the Week 22 visit and daily oral doses of placebo tablets from the Baseline visit until the Week 24 visit.

Randomization will be stratified by baseline disease severity (moderate validated Investigator Global Assessment for atopic dermatitis [vIGA-AD 3] vs. severe [vIGA-AD 4]) and age (< 40, ≥ 40 to < 65, ≥ 65 years). The subject's age at baseline will be used for randomization and throughout the duration of the study.

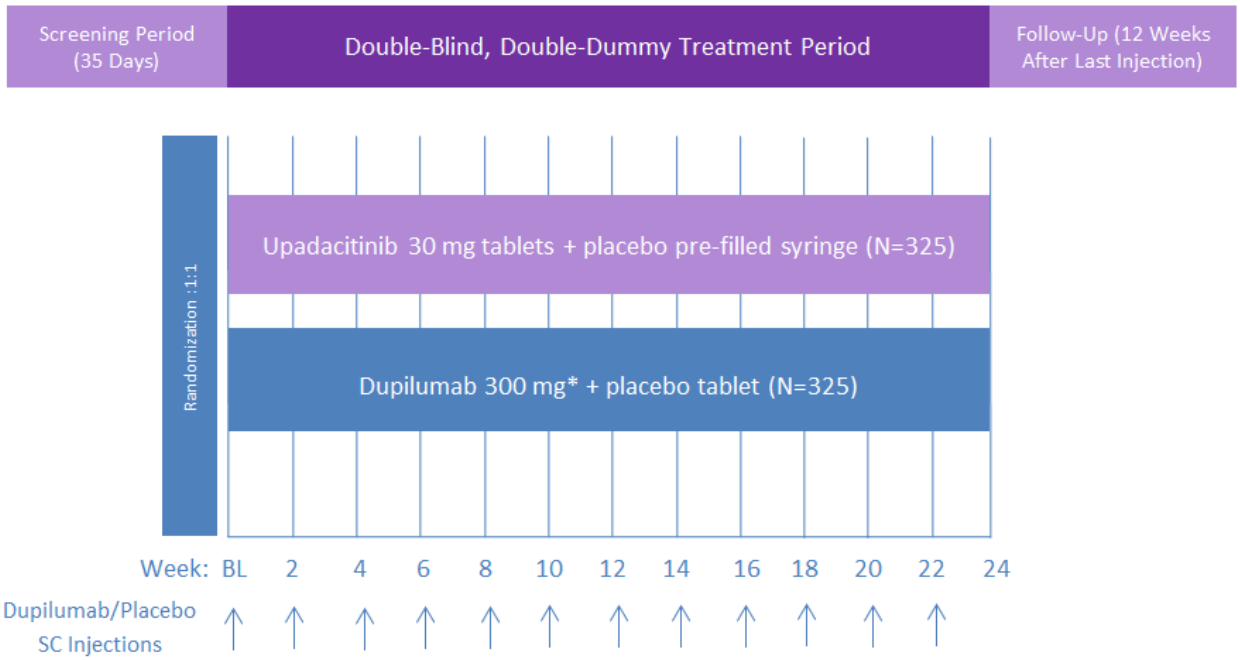
Information on the Data Monitoring Committee (DMC) and Cardiovascular Adjudication Committee (CAC) is described in Section 6.3.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in Section 5.10.

See Section 5.1 for information regarding eligibility criteria.

The study sites and subjects will remain blinded to treatment assignments for the duration of the study. A Week 24 database lock will occur after all ongoing subjects have completed the Week 24 visit; the Primary Analysis will be performed based on this database lock, which is the only and final analysis for efficacy. A final database lock will be performed at the end of the study.

Figure 1. Study Schematic



BL = Baseline; SC = subcutaneous

* Dupilumab 300 mg SC injection will be administered every other week starting at the Week 2 visit and until the Week 22 visit, after an initial dose of 600 mg at the Baseline visit.

4.2 Discussion of Study Design

Choice of Control Group

Dupilumab is a systemic therapy approved in the US, EU, and elsewhere for treatment of adult patients with moderate to severe AD. Indirect comparison of the upadacitinib Phase 2 study results with published results from the dupilumab Phase 3 studies shows superior nominal results for upadacitinib 30 mg QD versus dupilumab 300 mg every other week, in a similar patient population. This study is being performed to evaluate the hypothesis of potential superiority of upadacitinib.

Appropriateness of Measurements

Standard clinical and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with AD. Other than the biomarker analyses which are exploratory, all clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Eligible subjects have a documented history of inadequate response to treatment with topical or systemic AD treatments or they are subjects for whom topical treatments are otherwise medically inadvisable. As a result, these subjects have an unmet need for adequate control of their AD. Results in

the Phase 2 study that evaluated upadacitinib treatment for AD demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected dose (30 mg QD) compared to placebo in subjects with moderate to severe AD. Therefore, this subject population is considered appropriate for treatment and for evaluating a treatment difference between upadacitinib and dupilumab.

Selection of Doses in the Study

This study will evaluate upadacitinib (30 mg QD). The selection of this dose was informed by the analysis of the 16-week safety, efficacy, and exposure-response data of the Period 1 of the Phase 2 AD Study M16-048, which evaluated 3 doses of upadacitinib (7.5 mg, 15 mg, and 30 mg QD) versus placebo. In addition, all of the currently available pharmacokinetic, pharmacodynamic, safety, and efficacy data from upadacitinib studies were used to support the selection of these doses.

Study M16-048 Period 1 results demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected dose (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.

In addition, indirect comparison of the Phase 2 study results with published results from the dupilumab Phase 3 studies shows superior nominal results for upadacitinib 30 mg QD versus dupilumab 300 mg every other week, in a similar patient population. This study is being performed to confirm the hypothesis of potential superiority raised by this indirect comparison.

In summary, exposures associated with upadacitinib 30 mg QD using the once-daily formulation are predicted to be efficacious in treatment of subjects with moderate to severe AD with limited effects on laboratory parameters.

The selection of the dupilumab dose was based on the approved posology in moderate to severe atopic dermatitis subjects [initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection].[17,18]

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 ≥ 18 years old and ≤ 75 years old at Screening Visit.

- 2. Subjects and/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.
- 3. Subject is judged to be in general good health (other than AD) as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening.

AD Disease Activity

- 4. Chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria.[21]
- 5. 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 (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.
- 6. 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.
- 7. Documented history (within 6 months of the Baseline Visit) of inadequate response to TCS or topical calcineurin inhibitors (TCI) OR documented systemic treatment for atopic dermatitis within 6 months prior to the Baseline Visit, OR for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).

Contraception

- 8. Females of childbearing potential must have a negative 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).
- 9. 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 12-weeks after the last injection.
- 10. Female subject must not be pregnant, breastfeeding or considering becoming pregnant during the study or for approximately 12 weeks after the last injection.

- 11. Additional local requirements may apply. Refer to Section 5.10.

Prior and Concomitant Therapy

- 12. No prior exposure to any JAK inhibitor (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, abrocitinib [PF-04965842], and filgotinib).
- 13. No prior exposure to dupilumab.
- 14. 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-gamma (IFN-γ) and mycophenolate mofetil within 4 weeks;
  - Targeted biologic treatments (refer to Section 5.3) 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 6), including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days.
- 15. 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 12 weeks (or longer if required locally) after the last injection.
- 16. No systemic use of known strong cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to Table 1 in Section 5.3 for examples of commonly used strong CYP3A inhibitors and inducers).
- 17. 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.

Medical History

- 18. Laboratory values must not meet 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 m2 by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula;
  - Total white blood cell count (WBC) < 2,500/µL;

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

19. Subject must have no current or past history of infection including:
    - 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);
    - Human immunodeficiency virus (HIV) infection, defined as confirmed positive anti-HIV antibody (HIV Ab) test;
    - Active Tuberculosis (TB) or meets TB exclusionary parameters (refer to Section 5.10 for specific requirements for TB testing);
    - Non-skin related active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit;
    - Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
    - Active hepatitis B virus (HBV) or hepatitis C virus (HCV):
        - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects (and for hepatitis B surface antibody positive [+] where mandated per local requirements);
        - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
20. Subject must have no current or past history of the following medical conditions:
    - Any of the following cardiovascular conditions:
        - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting or moderate to severe congestive heart failure (New York Heart Association Class III or IV);
        - A confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
    - Any other unstable clinical condition which, in the opinion of the investigator, would put the subject at risk by participating in the protocol. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.

- 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 NMSC or localized carcinoma in situ of the cervix;
- History of clinically significant medical conditions or any other reason, which in the opinion of the investigator, would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study.

Miscellaneous

- 21. 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.
- 22. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.

5.2 Contraception Recommendations

Contraception Recommendations for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential
- Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, 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.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
  - Females who have not experienced menarche (at least one menstrual period).
- Females of Childbearing Potential
- Females of childbearing potential must avoid pregnancy while taking study drug and for at least 12 weeks after the last injection. Females must commit to one of the following methods of highly effective birth control:

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

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

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

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

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

5.3 Prohibited Medications and Therapy

JAK Inhibitors

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

Targeted Biologic Therapies

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

- abatacept
- adalimumab
- anakinra
- belimumab
- certolizumab
- efalizumab
- etanercept
- golimumab
- guselkumab
- infliximab
- ixekizumab
- natalizumab
- omalizumab
- rituximab
- secukinumab
- tocilizumab
- ustekinumab
- vedolizumab

Other Non-Biologic Systemic Therapy

Concomitant treatment with systemic non-steroidal systemic immunosuppressive drugs is prohibited during treatment with study drug, including but not limited to:

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

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

Corticosteroids

Concomitant treatment with systemic corticosteroids (oral, intravenous, intramuscular) and intralesional corticosteroids is prohibited during treatment with study drug.

Inhaled, ophthalmic drops and nasal corticosteroid formulations are allowed throughout the study.

See Rescue Therapy in Section 5.4 for further details on allowed 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 treatment with study drug.

Phototherapy, Tanning Booth, and Extended Sun Exposure

Ultra-violet (UV) B or UVA phototherapy including psoralen and ultraviolet A (PUVA) or laser therapy for at least 4 weeks prior to the Baseline visit and during the study are not allowed. 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 treatment with study drug.

Topical Therapy

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

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

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

Vaccines

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (per local label) at least 4 weeks (or longer if locally required) before first dose of study drug. Live vaccinations are prohibited during study participation until at least 12 weeks after the last injection.

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.

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

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

See Section 5.4 for information about permitted vaccines and recommendations for vaccines.

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.

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.

If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. See Section 5.7 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) that the subject is receiving at the time of screening, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF). Also, medications taken for atopic dermatitis since date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, route of administration.

If there are any questions regarding concomitant or prior therapies, the AbbVie TA SD should be contacted who will then discuss it with the AbbVie Therapeutic Area Medical Director (TA MD) and provide a recommendation.

Vaccines

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap). It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks before first dose of study drug or administered at least 12 weeks after the last injection. If the herpes zoster vaccine is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing 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 herpes zoster vaccine should not be administered. See Prohibited Medications/Therapy for a list of commonly used live vaccines that are prohibited during study participation.

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

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 for the duration of the study.

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.

Rescue Therapy

Rescue treatment for AD may be provided, if medically necessary at the discretion of the investigator.

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

Subjects who receive topical rescue treatment during the study treatment period can continue study drug.

If a subject needs rescue treatment with a systemic agent (including but not limited to corticosteroids, cyclosporine, methotrexate [MTX], mycophenolate mofetil, azathioprine) or phototherapy, study drug should be permanently discontinued prior to the initiation of rescue systemic agent or phototherapy.

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

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

5.5 Withdrawal of Subjects and Discontinuation of Study

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

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, gastrointestinal perforation, cardiovascular and thromboembolic events, malignancy, ECG abnormality, and select laboratory abnormalities.

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

- Rescue treatment is administered outside of the parameters described in Section 5.4 (Rescue Therapy).
- Initiation of any 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.
- Anaphylactic reaction or other severe systemic or local reaction to study drug injection.
- Abnormal laboratory results or AEs that neither meet the criteria for discontinuation of study drug, as stated in Section 6.2 or determined by the investigator and the AbbVie TA MD or TA SD rule out safe continuation of the study drug.
- 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 or TA SD.
- 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 or TA SD.

- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant or plans to become pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject develops a GI perforation.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial in consultation with the AbbVie TA MD or TA SD.
- 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 a change of QT interval corrected (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.

5.6 Follow-Up for Subject Withdrawal from Study

Discontinuation of Study Drug and Continuation of Study Participation

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment or study participation should complete a Premature Discontinuation visit (PD visit). 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.

Subjects who prematurely discontinue study drug but continue study participation should complete a PD visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix D and should adhere to all study procedures except for dispensing study drug. 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 End-End-of-Treatment 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 12 weeks after the last injection.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, an End-of-Treatment Follow-up visit or phone call may be completed 12 weeks after the last injection to ensure all treatment-emergent AEs and SAEs have been resolved.

Biomarker Research:

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 for the withdrawn subject or added to the existing data or database(s). Data generated for biomarker research before subject withdrawal of consent will remain part of the study results.

5.7 Study Drug

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug and Placebo

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib tablet	oral	Film-coated tablet	30 mg	AbbVie
Placebo tablet	oral	Film-coated tablet	NA	AbbVie
Dupilumab pre-filled syringe	SC	Solution for injection in pre-filled syringe	300 mg	Sanofi, Genzyme (Regeneron)
Placebo pre-filled syringe	SC	Solution for injection in pre-filled syringe	NA	AbbVie

The type and amount of kits dispensed will be managed by the Interactive Response Technology (IRT).

AbbVie will not supply drugs other than upadacitinib and dupilumab.

Storage and Disposition of Study Drug

Upadacitinib and placebo tablets must be stored at controlled room temperature (15° to 25°C/59° to 77°F).

Dupilumab and placebo pre-filled syringe must be stored refrigerated at 2°C to 8°C and protected from light, as specified on the label.

The investigational products are for investigational use only and are to be used only within the context of this study. The investigational products 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 on site as appropriate.

Upon receipt, study drugs should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via Interactive Response Technology (IRT) and encodes the appropriate study drugs to be dispensed at the subject's corresponding study visit. Study drugs must not be dispensed without contacting the IRT system. Study drugs will only be used for the conduct of this study.

Packaging and Labeling

Upadacitinib and placebo tablets will be packaged in bottles with quantities sufficient to accommodate the study design. Each bottle will be labeled per local requirements. The labels must remain affixed to the bottles. Each kit label will contain a unique kit number.

Dupilumab and placebo pre-filled syringes will be packaged in cartons with quantities sufficient to accommodate the study design. Each pre-filled syringe and carton will be labeled as required per country requirements. Labels must remain affixed to the syringe and carton. Each kit label will contain a unique kit number.

Dispense Study Drug

The type and amount of kits dispensed will be managed by the IRT. Dupilumab and placebo pre-filled syringe will be dispensed through IRT every 2 weeks, and upadacitinib and placebo tablets will be dispensed through IRT every 4 weeks.

Upadacitinib and placebo tablets 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 baseline (Day 1) procedures are completed. At the visits specified, the site personnel will review returned study drug kits and empty study drug packaging to verify compliance.

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.

Study Drug Administration

Upadacitinib or placebo tablets will be taken orally once daily 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. If a subject should forget to take upadacitinib or placebo tablet 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. Upadacitinib and placebo tablets should be swallowed whole and should not be split, crushed, or dissolved.

Dupilumab or placebo pre-filled syringe will be administered by SC injection at study visits on Day 1 and every other week at the study visits specified in Appendix D until Week 22.

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.

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

1. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow re-introduction 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.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects will be randomized in a 1:1 ratio to one of two treatment groups:

- Treatment A: Upadacitinib 30 mg + placebo pre-filled syringe (N = 325)
- Treatment B: Dupilumab 300 mg + placebo tablets (N = 325)

Randomization will be stratified by baseline disease severity (moderate [vIGA-AD 3] vs. severe [vIGA-AD 4]) and age (< 40, ≥ 40 to 65, ≥ 65 years).

Blinding

All AbbVie personnel with direct oversight of the conduct and management of the trial, with the exception of AbbVie Drug Supply Management Team, will remain blinded until the Week 24 database lock. All study site personnel involved in the study and the subjects will remain blinded to the 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. In addition, dupilumab pre-filled syringe and placebo pre-filled syringe will be administered to the subjects at the investigative site. Both types of pre-filled syringes will be provided in identical cartons. The cartons are sealed with tamper-evident seals. The study site personnel must not break the seals and open the cartons throughout the conduct of the study. The investigator will designate an unblinded administrator to administer the injection to the subject. The designated unblinded administrator must not have involvement with any other study-related activities.

To maintain the blind for the study, only the designated unblinded administrator will be allowed to break the tamper-evident seals of the cartons just prior to administration. If a kit of dupilumab/placebo is dispensed by IRT, it should remain sealed until the time of drug administration. If for any reason the study drug administration is not performed, the carton should remain sealed, and should be accounted and prepared for destruction without breaking the tamper evident seal, maintaining the blind of the study. Other study site personnel, including safety and efficacy evaluators, must not be involved with

administration of the injectable dosage forms. To maintain the blind for the subject, appropriate measures must be taken to ensure the subjects do not see the study drug syringe or subcutaneous administration of study drug. The investigational sites must take appropriate precautions, including, but not limited to, blindfolding the subject, creating a barrier between the subject and administrator or administration site, or by any other means of blinding the subjects. The unblinded administrator will immediately discard the syringe in an appropriate container after conducting administration and prior to removing the barrier between administrator and the subject.

Empty cartons without the syringe should be retained along with the unopened cartons for accountability. If the carton with the syringe has been opened (the tamper-evident seal broken) and the unblinded administrator is not able to administer study drug syringe for any reason, then the administrator must document the kit number and a reason(s) for not administering a specific kit. The unblinded administrator will immediately discard the syringe in an appropriate container after documenting accountability of such kit and prior to removing the barrier between administrator and the subject.

Other site personnel besides an unblinded administrator will not be made aware of the subject treatment assignments except in the event of an emergency where identification of the study drug is required for therapeutic measures. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

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

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

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.

Dupilumab and placebo pre-filled syringe dosing will be recorded on the designated eCRF. 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, and the accountability of the Study Drug/Placebo will be recorded in IRT.

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 independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

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, 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.

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 research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the exploratory research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study.

Screening and Re-Screening Procedures

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Operations Manual Section 2.1. With the exception of the QuantiFERON TB-Gold and purified protein derivative (PPD) tests (Tuberculosis Testing/Tuberculosis Prophylaxis below), otherwise exclusionary laboratory values can be re-tested once during the Screening Period. If the re-tested laboratory value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

Subjects who initially screen-fail for the study are permitted to re-screen once following re-consent. For additional re-screening, AbbVie TA MD or TA SD approval is required. As appropriate, sites are encouraged to contact the AbbVie TA MD/SD to confirm if subjects should or should not be re-screened. All screening procedures with the possible exceptions noted below will be repeated during re-screening.

The subject must meet all eligibility criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

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

- HBV, HCV and HIV serology
- QuantiFERON Tuberculosis [TB] Gold or equivalent and/or a PPD test (or both if required per local guidelines)
- CXR
- Electrocardiogram (ECG)

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 Bacille Calmette-Guérin (BCG) vaccination, cohabitation with individuals who have had TB, and travel to, reside in, or work in TB endemic locations.

Drug and Alcohol Screen

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

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.

Subjects will complete the following questionnaires (described below) as specified in Operations Manual Section 2.1: Worst Pruritus NRS; ADerm-IS; Head and Neck - Patient Global Impression of Severity (HN-PGIS), and Oral vs Injectable Questionnaire (only for the United States). The subject should complete the questionnaires before site personnel perform any clinical assessments and preferably before any interaction with site personnel has occurred to avoid biasing the subject's response.

A validated translation will be provided in their local language, as applicable. All PROs are collected electronically.

For the Worst Pruritus NRS, ADerm-IS, and HN-PGIS, the PRO instrument should be completed prior to drug administration on Day 1. All PRO instruments should be completed prior to any discussion of adverse events or any review of laboratory findings.

Worst Pruritus Numerical Rating Scale (NRS)

The Worst Pruritus NRS is an assessment tool that subjects use 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 daily from Screening through Week 16 using an electronic hand-held device that will be given to subjects to take home at Screening. Hand-held device usage ends at the Week 16 visit (subjects should provide their response on the site's tablet at the Week 16 study visit). Starting at the Week 16 visit, the frequency of administration will be reduced from daily assessments to assessments only at scheduled site visits using a tablet at the site.

Evaluation of the psychometric properties and assessment of the measurement validity of the Worst Pruritis NRS is pending Phase 3 data.

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 Baseline; devices will be given to subjects to take home at Screening.

Head and Neck Patient Global Impression of Severity (HN-PGIS)

The HN-PGIS asks subjects to describe the severity of their head and neck AD symptoms right now. Subjects rate their head and neck 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 HN-PGIS will be administered on the tablet at site visits throughout the study.

Oral vs Injectable Questionnaire (only in the United States)

The Oral vs Injectable Questionnaire is an assessment tool designed to assess subject preferences regarding route of administration (oral QD vs injection Q2 weeks) for medications for AD. The Questionnaire is administered at Week 24 at the site visit. Subjects provide responses to up to 5 questions using the electronic tablet device.

Investigator Assessment

The investigator assessments will be recorded on paper worksheets and entered into the eCRF and conducted at the study visits specified in Operations Manual Section 2.1. 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 assessor should evaluate the subject at each visit for the duration of the study. A back-up assessor should be identified. The 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 primary 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, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

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

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

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. It is recommended that the live herpes zoster vaccine should be considered for administration at least 4 weeks before first dose of study drug or administered at least 12 weeks after the last injection. If the herpes zoster vaccine is to be administered, and there is no known history of primary varicella (chicken pox), pre-existing 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 herpes zoster vaccine should not be administered. See Prohibited Medications/Therapy for a list of commonly used live vaccines that are prohibited during study participation.

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

Tuberculosis Testing/Tuberculosis Prophylaxis

The TB screening 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 questionnaire (Operations Manual Section 3.2) and tested for TB infection by QuantiFERON-TB Gold test. The site staff will complete the TB risk questionnaire for all subjects regardless of TB test results and enter the data into the appropriate eCRF. One or more "yes" response on the TB risk questionnaire indicates increased risk of TB.

If a subject had a negative PPD test within 90 days prior to Screening and a QuantiFERON-TB Gold test cannot be performed by the central laboratory at Screening and source documentation is available, TB testing by PPD Skin Test (also known as a TB Skin Test or Mantoux 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.

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 CXR 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 CXR. Subjects with no signs or symptoms and a CXR 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.

If an annual TB test is newly positive (seroconversion), a CXR needs to be performed as soon as possible to aid in distinguishing active versus latent TB and subsequent annual TB follow-up tests are not required. Any positive TB test after the patient 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 investigation and a repeat test before the next scheduled annual TB retest, the case (including the TB test results) should be discussed with the AbbVie TA MD.

TB test

- The QuantiFERON-TB Gold test (or equivalent) should be performed at Screening on all subjects. The PPD skin test should be utilized when the QuantiFERON-TB Gold test (or equivalent) is not possible or if both tests are required per local guidelines.
- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test and/or PPD skin test 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, both will be performed. If either PPD or QuantiFERON-TB Gold is positive, the TB test is considered positive.
- The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold 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 alone, then the subject should have their annual TB test performed with a QuantiFERON-TB Gold test.
- If the QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold 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 PPD in the past should not be re-exposed and the PPD should be considered positive.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (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 patient is considered to be negative.
- In cases where the QuantiFERON-TB Gold test by the central laboratory is positive and the investigator considers the subject at low risk for TB and has no clinical suspicion of TB, the investigator may perform a local QuantiFERON-TB Gold test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive, the test is considered positive.
- An equivalent Interferon Gamma Release Assay (IGRA) (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold.

TB prophylaxis

Note: Rifampicin and Rifapentine are not allowed for 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 must be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

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 should not be withheld. Two to four 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 CXR will not be required if the subject had a previous normal CXR (posterior-anterior and lateral views) within 90 days of Screening, provided all source documentation is available at the site, as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test.

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 Screening (Operations Manual Section 2.1). 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

Biomarker Sampling

Optional biospecimens (blood, serum, plasma, and skin biopsies) will be collected for biomarker research 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. The samples may be retained while research on upadacitinib (or drugs of this class) or atopic dermatitis and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Height and Body Weight

Height and body weight will be measured without shoes at visits specified in Appendix D. 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, and body temperature will be obtained at visits specified in Appendix D. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes. For additional guidance on conventional office blood pressure measurements, please refer to the 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines.[22]

Physical Examination

A complete physical examination will be performed at visits specified in Appendix D. The physical examination performed on Study Day 1 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.

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), due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

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

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

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

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

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

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

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr><td>Hematocrit
Hemoglobin
RBC count
WBC count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count</td><td rowspan="2">BUN
Creatinine
Total bilirubin
INR (reflex only)[a]
Albumin
ALT
AST
Alkaline phosphatase
CPK
Sodium
Potassium
Bicarbonate/CO_2
Chloride
Calcium
Inorganic phosphorus
Uric acid
Total protein
Glucose
Cholesterol
LDL-C
HDL-C
Triglycerides</td><td rowspan="2"><u>Central Lab Tests:</u>
Estimated glomerular filtration rate (eGFR)
International normalized ratio (INR)
Serum pregnancy (beta human chorionic gonadotropin [bHCG]) test
<u>Hepatitis Screening:</u>
Hepatitis B surface antigen (HBs Ag)
Hepatitis B surface antibody (HBs Ab)
Hepatitis B core antibody (HBc Ab)
Hepatitis B virus deoxyribonucleic acid polymerase chain reaction (HBV DNA PCR [reflex only])
Hepatitis C virus antibody (HCV Ab)
Hepatitis C virus ribonucleic acid (HCV RNA [reflex only])
Human immunodeficiency virus antibody (HIV Ab)
QuantiFERON-TB Gold
High-sensitivity C-reactive protein (hsCRP)
Follicle stimulating hormone (FSH)[b]
Drug and alcohol screen
<u>Local Lab Tests:</u>
Urine pregnancy test
Varicella antibody, if indicated
PPD test/T-SPOT TB</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 only for female < 55 years old.

Pregnancy Tests (Serum and Urine)

A serum pregnancy test will be performed for female 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;
- Negative, the subject can be enrolled into the trial;

- Still borderline ≥ 3 days later, the subject is considered a screen failure.

A urine pregnancy test will be performed for all female of childbearing potential at the Baseline Visit prior to the first dose of study drug and at minimum at monthly intervals at study visits. More frequent pregnancy tests will be performed throughout the study if required per local requirements. If the End-of-Treatment follow up period is longer than 30 days, female subjects should perform monthly pregnancy tests at home, and the results of the monthly at home tests should be communicated to the site.

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin.
- If the baseline or post-baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be performed by the central laboratory. If the serum pregnancy test is negative, study drug may be started or resumed. If the serum pregnancy test is positive, study drug must be permanently discontinued. In the event a pregnancy test comes back borderline, a repeat test is required (≥ 3 days later) to document a negative result. 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, the subject must be discontinued.

If during the course of the study a female becomes surgically sterile or post-menopausal and complete documentation as described in *Contraception Recommendations* for Female 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.

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 (HBV):

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

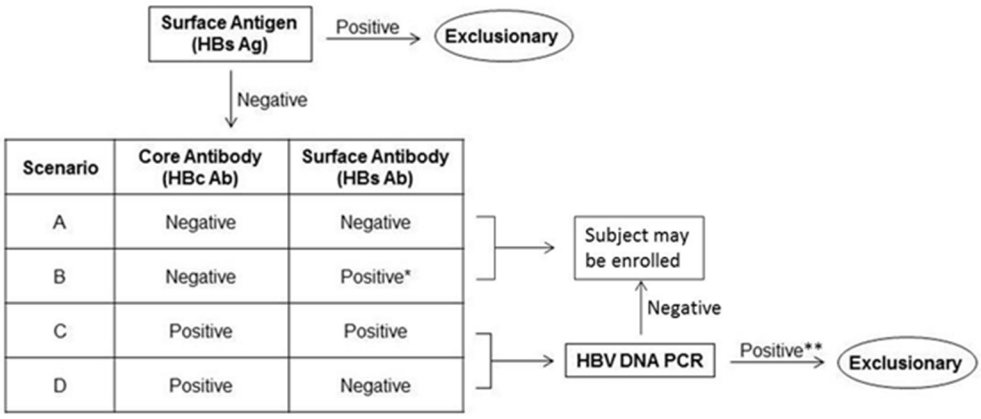
- HBs Ag (Hepatitis B surface antigen)
- HBc Ab/anti-HBc (Hepatitis B core antibody)
- HBs Ab/anti-HBs (Hepatitis B surface antibody)

A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will trigger automatic reflex testing for 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 a 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).*
- For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab requires HBV DNA PCR testing (automatic reflex testing; 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 for HBV DNA that exceeds detection sensitivity will be considered positive.

Figure 2. Interpretation and Management of HBV Serologic Test Results



* A positive test result for HBs Ab is expected for subjects who have had a HBV vaccination. For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab 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 every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab.

- A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.

    - A subject with a negative result for HBV DNA testing may be enrolled.
- Where mandated by local requirements: A positive result for HBs Ab requires HBV DNA PCR testing.
    - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
    - A subject with a negative result for HBV DNA may be enrolled.
    - For subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening, HBV DNA PCR test should be performed every 12 weeks. HBV DNA PCR testing 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.

Hepatitis C Virus (HCV)

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

Human Immunodeficiency Virus (HIV)

Subjects with HIV infection (positive HIV test) are excluded from study participation. An anti-HIV antibody (Ab) test 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. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Discontinuation of Study Drug and Subjects Withdrawal

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 should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

Discontinuation of Study Drug and Continuation of Study Participation

Subjects may discontinue study drug treatment but may choose to continue to participate in the study. A subject who discontinues one treatment (injection or tablet) will be discontinued from the other treatment (tablet or injection). 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 should adhere to all study procedures except for annual TB testing, dispensing study drug, and blood sample collection for optional exploratory research and validation studies. Once the subject has discontinued study drug, all rescue and efficacy driven discontinuation criteria no longer apply, and subjects should be treated per standard of care. 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 (discontinuation of study drug treatment and study participation; withdrawal of informed consent) for any reason at any time. If a subject prematurely discontinues study participation, the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, an End-of-Treatment Follow-up visit or phone call may be completed 12 weeks after the last injection to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. Subjects who discontinue the study prematurely after randomization will not be replaced.

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.

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 adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

If any of the following events are reported, then the following supplemental report must be completed:

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

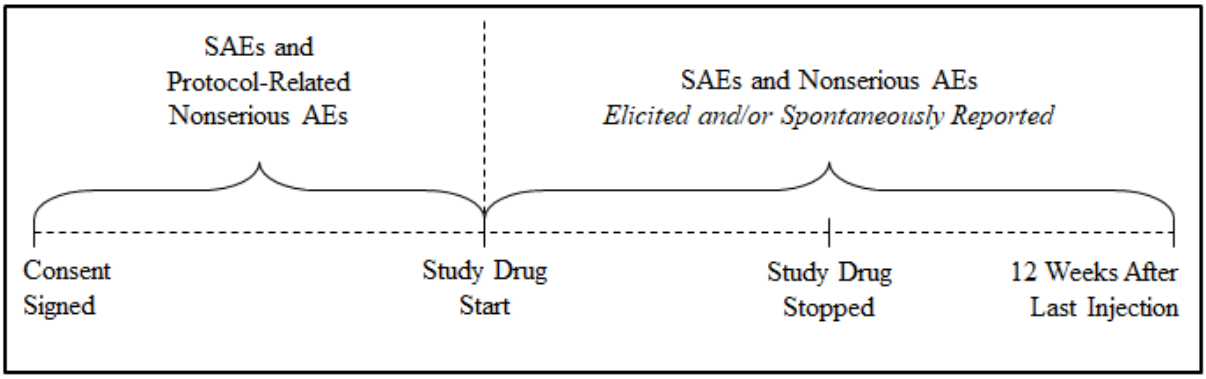
If an adverse event meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or Contract Research Organization (CRO) (as appropriate) as a serious adverse event within 24 hours of the site being made aware of the serious adverse event:

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 adverse events reported from the time of study drug administration until 12 weeks after the last injection will be collected, whether solicited or spontaneously reported by the subject. Subjects who discontinue study drug treatment but continue to participate in the study will have AEs collected for the remainder of study participation. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signs the study-specific informed consent.

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



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

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

Adverse Events of Special Interest

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

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

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

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

Severe (Grade 3 - 5)

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

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

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

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

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

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

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 12 weeks after the last injection. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

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

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 12 weeks after the last injection) 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 adverse event 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 Events of 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 (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: [redacted]
FAX to: + [redacted]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Office:
Email: [redacted]

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

Primary Therapeutic Area Medical Director

[redacted]

AbbVie Inc.

[redacted]

1 North Waukegan Road

North Chicago, IL 60064

Contact Information:

Office: [redacted]

Mobile:

Email:

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: [redacted]	

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

6.2 Toxicity Management

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

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

Management of Hypersensitivity

Subjects should be closely monitored and assessed for the development of signs and symptoms of hypersensitivity reactions, including anaphylaxis. Study drug should be interrupted and appropriate therapy be instituted if a subject develops clinically significant hypersensitivity reactions.

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 gastrointestinal perforation should be evaluated promptly for early diagnosis and treatment. If the diagnosis of gastrointestinal 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 the study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Management of 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 Fridericia's correction formula (QTcF) value > 500 msec, OR a change of QTc interval > 60 msec from baseline.

Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 3 and may require a supplemental eCRF to be completed (see Protocol Section 6.1 [Complaints and Adverse Events]). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 3, the repeat testing must occur as soon as possible.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with new sample • If hemoglobin decreases ≥ 3.0 g/dL from baseline, without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, 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 if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5.
	• A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from baseline).
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• Interrupt study drug if confirmed ALT or AST > 8 × ULN by repeat testing with new sample.
	• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Screening who develop the following should have HBV DNA PCR testing performed within one week (based on initial elevated value):
	  • ALT> 5 × ULN OR
	  • ALT or AST > 3 × ULN if an 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 and ALT or AST elevations persist.
	For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

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

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.

The operation of the DMC data review involves data preparation by AbbVie (for blinded data) and an independent CRO (Axio Research for unblinded data to DMC), DMC review of the data at a prespecified schedule (every 4 months) or ad hoc if needed, DMC report with recommendations provided to the AbbVie Contact, and triage of the recommendations the AbbVie Contact to the appropriate parties (AbbVie Study Management Team or Internal Review Committee). The first DMC meeting is expected to occur approximately 4 months after the first subject first dose date.

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. In addition, the treatment outcomes will not be communicated from the DMC to the Study Teams.

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

6.4 Other Safety Data Collection

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

6.5 SUSAR Reporting

AbbVie will be responsible for 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 DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

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

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the Week 24 database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Intent-to-Treat (ITT) Population consists of all randomized subjects and will be used for the efficacy analyses. A Per-Protocol Population may be defined if deemed necessary to exclude subjects with protocol violations that will affect the primary endpoint. If defined, the criteria to determine the Per-Protocol Population will be detailed in the SAP. List of subjects to be excluded from the Per-Protocol Population will be finalized before database lock and blind break. The Per-Protocol Population, if defined, will be used to analyze the primary efficacy endpoint.

The Safety Population consists of all randomized subjects who received at least 1 dose of study drug including placebos.

7.3 Statistical Analyses for Efficacy

All efficacy endpoints will be analyzed in the ITT population to test the superiority of upadacitinib over dupilumab. In addition, the primary efficacy endpoints will be analyzed in the Per Protocol Population, if defined. Subjects will be included in the treatment group to which they are randomized.

Categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by vIGA-AD categories (vIGA-AD 3 or 4). Continuous variables will be analyzed using mixed-effect model with repeated measures (MMRM).

Missing values and visits after the rescue will be handled by non-responder imputation (NRI) for categorical variables (except for missing values due to COVID-19, which will be handled by multiple imputation, NRI-C) or MMRM for continuous variables.

Primary Analysis

The primary endpoint is the proportion of subjects achieving EASI 75 at Week 16.

Comparison of the primary endpoint will be made between the upadacitinib group and the dupilumab group using the CMH test, stratified by vIGA-AD categories. NRI-C will be the primary approach to handle missing values, with multiple Imputation (MI) as the sensitivity approach to handle missing values. Per-protocol analysis, if defined, will be used as another sensitivity analysis.

Secondary endpoints will be analyzed in the ranked order as outlined in Section 3.3.

Sample Size Estimation

Approximately 650 subjects (18 - 75 years old) will be randomized to upadacitinib 30 mg or dupilumab in a ratio of 1:1 (325 subjects per treatment group). Assuming an EASI 75 response rate of at most 50% in the dupilumab arm, this sample size will provide more than 80% power to detect at least a 12% treatment difference using two-sided test at a 0.05 significant level. The assumption of dupilumab response rate for EASI 75 at Week 16 and 12% treatment difference were based on the pooled response rates of dupilumab Phase 3 monotherapy studies (SOLO 1 and SOLO 2) and the response rate of upadacitinib 30 mg in the upadacitinib AD Phase 2b study.[23]

7.4 Statistical Analyses for Safety

The safety analyses will be carried out using the Safety Population 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 MedDRA. Treatment-emergent AEs (TEAEs) are defined as those that began or worsened in severity after the first dose of study drug and no more than 5 half-lives of the drug after the last dose of study drug. Specifically, 30 days will be used for upadacitinib, and 84 days (12 weeks) will be used for dupilumab. 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, 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 subject with evaluations meeting criteria for pre-defined Potentially Clinically Significant values will be summarized.

7.5 Statistical Analysis of Optional Proteomic Biomarker Data

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

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

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

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 patient reported outcome design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health. Daily Worst Pruritus NRS and daily and weekly ADerm-IS ePROs will be collected from subjects electronically every evening via a hand-held device provided to the subject at Screening. Hand-held device usage stops at the Week 16 visit. The Week 16 and subsequent NRS will be completed electronically via an onsite tablet device. ADerm-IS will be collected only during the Screening period and at the Baseline Visit. The hand-held electronic device will be programmed to allow data entry once per day. The ePRO data of HN-PGIS 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 Oral vs Injectable Questionnaire will be collected electronically from subjects via the onsite tablet device at the Week 24 visit (only performed in the United States). 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.

12 REFERENCES

1. Kunz B, Oranje AP, Labrèze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology. 1997;195(1):10-9.
2. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018;32(5):657-82.
3. Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. Pediatrics. 2008;122(4):812-24.
4. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergoly and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy. 2006;61(8):969-87.
5. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-49.
6. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389(10086):2287-303.
7. Simpson EL, Bieber T, Guttman-Yaasky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335-48.
8. Chung-Ching C, Di Meglio P, Nestle FO. Harnessing dendritic cells in inflammatory skin diseases. Semin Immunol. 2011;23(1):28-41.
9. Nobbe S, Dziunycz P, Muhleisen B, et al. IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. Acta Derm Venereol. 2012;92(1):24-8.
10. Genovese MC, Smolen JS, Weinblatt ME, et al. Efficacy and Safety of ABT-494, a Selective JAK-1 Inhibitor, in a Phase IIb Study in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate. Arthritis Rheumatol. 2016;68(12):2857-66.
11. Kremer JM, Emery P, Camp HS, et al. A Phase IIb Study of ABT-494, a Selective JAK-1 Inhibitor, in Patients With Rheumatoid Arthritis and an Inadequate Response to Anti–Tumor Necrosis Factor Therapy. Arthritis Rheumatol. 2016;68(12):2867-77.
12. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet Online. 2018;391(10139):2513-24.
13. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Online. 2018;391(10139):2503-12.

14. AbbVie. Upadacitinib Investigator's Brochure Edition 10. 19 August 2019.
15. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116-32.
16. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32(6):850-78.
17. Dupixent [summary of product characteristics]. Paris, France: Sanofi-Aventis Groupe. 2017.
18. Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2017.
19. Banerjee S, Biehl A, Gadina M, et al. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs. 2017;77(5):521-46.
20. Norman P. Selective JAK1 inhibitor and selective Tyk2 inhibitor patents. Expert Opinion on Therapeutic Patents. 2012;22(10):1233-49.
21. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;944-47.
22. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104.
23. Simpson EL, Bieber T, Guttman-Yassky E, at al. SOLO 1 and SOLO 2 Investigators. Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. NEJM. 2016;375(24):2335-48.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
AD	Atopic dermatitis
ADerm-IS	Atopic dermatitis impact scale
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AxSpA	Axial spondyloarthritis
BCG	Bacille Calmette-Guérin
BSA	Body surface area
BUN	blood urea nitrogen
CAC	Cardiovascular adjudication committee
CD	Crohn's disease
CFR	Code of Federal Regulations
CLDN1	Claudin 1
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPK	Creatine kinase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest x-ray
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI 75/90/100	75%/90%/100% reduction in Eczema Area and Severity Index

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
ePRO	Electronic patient reported outcome
EU	European Union
EudraCT	European Clinical Trials Database
FLG	Filaggrin
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBc	Anti-hepatitis B core antibodies
HBc Ab	Hepatitis B core antibodies
HBs	Anti-hepatitis B surface antibody
HBs Ab	Anti-hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C antibody
HDL-C	high-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
HLA	Human Leukocyte Antigen
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFN	interferon
IFN-γ	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IGRA	Interferon-gamma release assay
IL	Interleukin

IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JAK	Janus kinase
LDL-C	low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	mixed-effect model with repeated measures
MTX	Methotrexate
NCI	National Cancer Institute
NK	Natural killer
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
NRI-C	Non-Responder Imputation incorporating Multiple Imputation to handle missing data due to COVID-19
NRS	Numerical rating scale
PCR	Polymerase chain reaction
PD	Premature discontinuation
PDE4	Phosphodiesterase type 4
PGIS	Patient Global Impression of Severity
PPD	Purified protein derivative
PRO	patient-reported outcome
PsA	Psoriatic arthritis
PT	Preferred term
PUVA	Psoralen and ultraviolet A
QD	Once daily
QTc	QT interval corrected

QTcF	Friedericia's correction formula
RA	Rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SOC	System organ classes
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
Tdap	Tetanus-diphtheria-acellular pertussis
TEAE	Treatment emergent adverse event
TNF	tumor necrosis factor
Tyk2	Tyrosine kinase 2
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
UV	Ultra violet
vIGA-AD	Validated Investigator Global Assessment for atopic dermatitis
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-046: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 10 November 2020

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Immunology Clinical Development
		Immunology Clinical Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Pharmacovigilance & Patient Safety
		Immunology Translational Science
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the Operations Manual Section 2.1.

Study Activities Table

Activity	Screening	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Un-scheduled Visit for Rescue Treatment	PD Visit	F/U Visit (12 Wks After Last Injection)
INTERVIEWS & QUESTIONNAIRES																		
Subject information and informed consent	✓																	
Eligibility criteria	✓	✓																
Medical/surgical history	✓	✓																
Alcohol and nicotine use	✓																	
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk assessment form	✓																	
Review pregnancy avoidance recommendations (females of childbearing potential only)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PRO																		
Worst Pruritus NRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ADerm-IS	✓	✓																
HN-PGIS	✓	✓	✓	✓	✓		✓		✓		✓		✓		✓			
Oral vs Injectable Questionnaire (US only)															✓			
EXAMS and Local Labs																		
Body Weight	✓	✓			✓						✓				✓	✓	✓	
Height	✓																	
Vital Signs (at FU if needed to monitor AEs)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)

Activity	Screening	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Un-scheduled Visit for Rescue Treatment	PD Visit	F/U Visit (12 Wks After Last Injection)
Physical Exam (at FU if needed to monitor AEs)	✓	✓			✓						✓				✓			(✓)
12-lead ECG	✓																	
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator Assessment vIGA	✓	✓																
Investigator Assessment EASI, BSA	✓	✓	✓	✓	✓		✓		✓		✓		✓		✓	✓	✓	
Chest x-ray for TB assessment	✓																	
Urine pregnancy test (for all female subjects of childbearing age)		✓			✓		✓		✓		✓		✓		✓			
CENTRAL LABS																		
Serum pregnancy test (for all female subjects of childbearing age)	✓																	
hsCRP, clinical chemistry, hematology, urinalysis	✓	✓		✓	✓		✓		✓		✓		✓		✓	✓	✓	✓ (only as needed for AEs)
Drug and alcohol screen	✓																	
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)	✓																	
HIV, HBV, and HCV	✓																	
Total Serum IgE		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Whole Blood for RNA		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Whole blood (plasma for proteomic and targeted protein investigations)		✓	✓	✓			✓				✓				✓			

Activity	Screening	Baseline Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Un-scheduled Visit for Rescue Treatment	PD Visit	F/U Visit (12 Wks After Last Injection)
Optional Biomarker: Whole blood (serum for proteomic and targeted protein investigations)		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Whole blood for DNA		✓	✓	✓			✓				✓				✓			
Optional Biomarker: Lesional/nonlesional skin biopsies		✓		✓							✓							
℞ TREATMENT																		
Randomization/drug assignment		✓																
Administration of Injectable study drug/placebo; retain unused carton sealed or empty carton without syringe.		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Dispense study drug		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Perform blinded drug accountability and reconciliation, retain unused carton sealed or empty carton without syringe (instruction for retaining cartons is not relevant to Week 24, Un-scheduled Visit, or PD Visit).				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Protocol	Date
Version 1.0	17 October 2018
Version 1.1 (VHP Countries: Czech Republic, Denmark, Finland, Germany, Hungary, Italy, Norway, Poland, Spain, Sweden, United Kingdom)	18 February 2019
Version 1.2 (Ireland only)	18 February 2019
Administrative Change 1	31 May 2019
Version 1.3 (United States only)	25 June 2019
Version 2.0	13 March 2020
Version 2.1 (Ireland only)	13 March 2020
Version 2.2 (VHP countries)	31 July 2020
Version 3.0	28 October 2020
Version 2.2.1 (VHP countries)	29 October 2020

Summary of Protocol Changes:

- Section 4.1 Overall Study Design and Plan
  - Specified that a Week 24 database lock will be conducted to perform the Primary Analysis.

  Rationale: To clarify the timing of the Primary Analysis.
- Section 5.8 Randomization/Drug Assignment
  - Clarified that AbbVie personnel will remain blinded until the Week 24 database lock.

  Rationale: To be consistent with Section 4.1.
- Section 7.1 Statistical and Analytical Plans
  - Specified that the SAP will be finalized prior to the Week 24 database lock.

  Rationale: To be consistent with Section 4.1.

APPENDIX F. OPERATIONS MANUAL

abbvie

Operations Manual for Clinical Study Protocol M16-046

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

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

FULL TITLE: A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064 **umber:** [redacted]
Safety Concerns	Immunology Safety Team [redacted] 1 North Waukegan Road North Chicago, IL 60064
SAE Reporting outside of RAVE	Email: [redacted]
Protocol Deviations	[redacted] AbbVie Inc. 41-45 Marinou Antypa Street 141 21 N. Irakleio Athens, Greece
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214
Biomarker Sample Storage	BioStorage Technologies Inc 2910 Fortune Circle West, Suite E Indianapolis, IN 46241

abbvie

TABLE OF CONTENTS

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. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

Activities are grouped by category: Interviews and Questionnaires, Patient Reported Outcomes (PRO), Exam, Local Lab, Central Lab, and Treatment. Further information about each activity is provided in Section 5.10 of the protocol.

SCREENING:

INTERVIEWS & QUESTIONNAIRES	• Subject Information and Informed consent[a] • Eligibility criteria • Medical/surgical history	• Alcohol and nicotine use • Prior/concomitant therapy • Latent Tuberculosis (TB) risk factor questionnaire
PRO	• Worst Pruritus Numerical Rating Scale (NRS) • Atopic Dermatitis Impact Scale (ADerm-IS)	• Head and Neck Patient Global Impression of Severity (HN-PGIS) • Dispense subject hand-held device
EXAM	• Body weight • Height • Vital signs • Physical examination • 12-lead Electrocardiogram (ECG)[b] • Adverse event (AE) assessment[c]	• Investigator Assessments: Eczema Area and Severity Index (EASI), body surface area (BSA), validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) • Chest x-ray for TB assessment
CENTRAL LAB	• Serum pregnancy test (for all female subjects of childbearing potential)[f] • Follicle stimulating hormone (FSH)[g] • High sensitivity C-reactive protein (hsCRP) • Clinical Chemistry • Hematology • Urinalysis • Drug and alcohol screen	• TB Test (QuantiFERON TB Gold test [or interferon gamma release assay (IGRA) equivalent such as T-SPOT test] and/or local purified protein derivative [PPD] skin test, if required)[d] • Human immunodeficiency virus (HIV),[e] hepatitis B (HBV), and hepatitis C (HCV) Screening

a. Obtain informed consent prior to performing any study-related procedures.
b. The ECG obtained at Screening will serve as the Baseline reference. Screening ECG not required if subject had normal ECG within 90 days of Screening (refer to Section 5.10 of the protocol for additional details).
c. Only serious adverse events (SAEs) and protocol-related nonserious AEs collected at Screening (refer to Section 6 of the protocol for additional details).
d. The QuantiFERON-TB Gold test (or equivalent) should be performed on all subjects. The PPD skin test should be utilized when the QuantiFERON-TB Gold test (or equivalent) is not possible or if both tests are required per local guidelines.
e. Anti-HIV antibody (Ab) performed at Screening, unless prohibited by local regulations (refer to Section 5.10 of the protocol for additional details).
f. For all females of childbearing potential (refer to Section 5.10 of the protocol for additional details).

g. FSH tested at Screening if female subject is ≤ 55 years of age AND has had no menses ≥ 12 months AND has no history of permanent surgical sterilization (refer to Section 5.10 of the protocol for additional details).

BASELINE/DAY 1:

INTERVIEWS & QUESTIONNAIRES	• Eligibility criteria • Medical/surgical history • Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS • ADerm-IS	• HN-PGIS • Subject hand-held device review
EXAM	• Body weight • Vital signs • Physical exam	• AE assessment • Investigator Assessments (EASI, BSA, vIGA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total immunoglobulin E (IgE) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA • Optional Biomarker: Lesional/nonlesional skin biopsies
TREATMENT	• Randomization/drug assignment • Dispense study drug	• Administration of injectable study drug/placebo • Retain unused carton sealed, or empty carton without the syringe

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

WEEK 1:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
CENTRAL LAB	• Total IgE • Optional Biomarker: Whole blood RNA • Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum)	• Optional Biomarker: Whole blood DNA

WEEK 2:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
CENTRAL LAB	• Total IgE • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA • Optional Biomarker: Lesional/nonlesional skin biopsies
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 4:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS • HN-PGIS	• Subject hand-held device review
EXAM	• Body weight • Vital signs • AE assessment	• Physical exam • Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 6:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• Subject hand-held device review
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 8:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total IgE (serum) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 10:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• Subject hand-held device review
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 12:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device review
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 14:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• Subject hand-held device review
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 16:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS • Subject hand-held device return and review
EXAM	• Body weight • Vital signs • AE assessment	• Physical exam • Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total IgE (serum) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA • Optional Biomarker: Lesional/nonlesional skin biopsies
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 18:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 20:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	• HN-PGIS
EXAM	• Vital signs • AE assessment	• Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 22:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	
EXAM	• Vital signs	• AE assessment
TREATMENT	• Dispense study drug • Administration of injectable study drug/placebo	• Retain unused carton sealed, or empty carton without the syringe • Perform blinded drug accountability and reconciliation

WEEK 24:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS • Oral vs Injectable Questionnaire (United States only)	• HN-PGIS
EXAM	• Body weight • Vital signs • AE assessment	• Physical exam • Investigator Assessments (EASI and BSA)
LOCAL LAB	• Urine pregnancy test for all female subjects of childbearing potential	
CENTRAL LAB	• Total IgE (serum) • hsCRP • Clinical Chemistry • Hematology • Urinalysis • Optional Biomarker: Whole blood RNA	• Optional Biomarker: Whole blood for proteomic and targeted protein investigations (plasma and serum) • Optional Biomarker: Whole blood DNA
TREATMENT	• Perform blinded drug accountability and reconciliation	

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	
EXAM	• Body weight • Vital signs	• AE assessment • Investigator Assessments (EASI and BSA)
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Perform blinded drug accountability and reconciliation	

PREMATURE D/C VISIT:

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	• Review and document pregnancy avoidance recommendations with females of childbearing potential
PRO	• Worst Pruritus NRS	
EXAM	• Body weight • Vital signs	• AE assessment • Investigator Assessments (EASI and BSA)
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis
TREATMENT	• Perform blinded drug accountability and reconciliation	

F/U VISIT (12 Weeks After Last Injection):

INTERVIEWS & QUESTIONNAIRES	• Prior/concomitant therapy	
EXAM	• AE assessment	
CENTRAL LAB	• hsCRP • Clinical Chemistry	• Hematology • Urinalysis

Notes: A Follow-Up Visit will occur approximately 12 weeks after the last injection to obtain additional safety information. If the follow up period is longer than 30 days, female subjects should perform monthly pregnancy tests at home, and the results of the monthly at home tests should be communicated to the site. For subjects who prematurely discontinued study participation and are willing to provide additional information, this visit may be a telephone call if a site visit is not possible. The Follow-Up Visit is not applicable for subjects who discontinued study drug and continued study participation with completion of at least one study visit occurring at least 12 weeks after the last injection.

Vital signs, physical examination, and clinical laboratory collections should only be made at Follow-Up if needed to continue monitoring of relevant AEs.

3 APPENDICES

3.1 STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
AD	Atopic dermatitis
ADerm-IS	Atopic dermatitis impact scale
AE	Adverse event
BSA	Body surface area
DNA	Deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EU	European Union
FSH	Follicle-stimulating hormone
F/U	Follow-up
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HN-PGIS	HN-PGIS
hsCRP	High-sensitivity C reactive protein
IGRA	Interferon gamma release assay
IgE	Immunoglobulin E
NRS	Numerical rating scale
PPD	Purified protein derivative
PRO	Patient reported outcome
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
TB	Tuberculosis
vIGA-AD	Validated Investigator Global Assessment for atopic dermatitis

3.2 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

3.3 WORST 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

abbvie

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

Instructions: The following questions are about your atopic dermatitis (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 atopic dermatitis (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 0 1 2 3 4 5 6 7 8 9 10 Extremely limited ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
7.	During the past seven days, how **difficult** was it for you **to concentrate** due to AD?	Not difficult 0 1 2 3 4 5 6 7 8 9 10 Extremely difficult ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8.	During the past seven days, how **self-conscious** did you feel due to AD?	Not self-conscious 0 1 2 3 4 5 6 7 8 9 10 Extremely self-conscious ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
9.	During the past seven days, how **embarrassed** did you feel due to AD?	Not embarrassed 0 1 2 3 4 5 6 7 8 9 10 Extremely embarrassed ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
10.	During the past seven days, how **sad** did you feel due to AD?	Not sad 0 1 2 3 4 5 6 7 8 9 10 Extremely sad ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

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

3.5 HEAD AND NECK - PATIENT GLOBAL IMPRESSION OF SEVERITY (HN-PGIS) QUESTIONNAIRE EXAMPLE

HEAD AND NECK - PATIENT GLOBAL IMPRESSION OF SEVERITY (HN-PGIS)

Seven point response scale

Please mark an "X" in the box (☒) that best describes the severity of your atopic dermatitis (AD) symptoms right now for **only your head and neck**.

5. Right now, my atopic dermatitis (AD) symptoms for my **head and neck** 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.

3.6 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.

3.7 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.

3.8 ORAL VS INJECTABLE QUESTIONNAIRE (United States only)

[redacted]

Document Approval

Study M16046 - A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis - Operations Manual for Protocol Version 4-0 - 10Nov2020

Version: 1.0 **Date:** 11-Nov-2020 02:27:30 PM **Company ID:** 11112020-00F9F6848D4CCE-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	11-Nov-2020 12:55:35 AM	Approver
	11-Nov-2020 01:02:14 AM	Approver
	11-Nov-2020 01:36:10 AM	Approver
	11-Nov-2020 02:06:32 A	Approver
	11-Nov-2020 07:48:05 AM	Approver
	11-Nov-2020 12:39:36 PM	Approver
	11-Nov-2020 01:21:36 P	Author
	11-Nov-2020 02:27:30 PM	Approver

Document Approval

Study M16046 - A Phase 3b Multicenter, Randomized, Double-Blind, Double-Dummy, Active Controlled Study Comparing the Safety and Efficacy of Upadacitinib to Dupilumab in Adult Subjects with Moderate to Severe Atopic Dermatitis - Protocol Version 4-0 - EudraCT 2018-002264-57 - 10Nov2020

Version: 1.0 **Date:** 11-Nov-2020 02:27:33 PM **Company ID:** 11112020-00F9F6848D4CCF-00001-en

Signed by:	Date:	Meaning Of Signature:
[redacted]	11-Nov-2020 12:55:35 AM	Approver
	11-Nov-2020 01:02:14 AM	Approver
	11-Nov-2020 01:36:10 AM	Approver
	11-Nov-2020 02:06:32 A	Approver
	11-Nov-2020 07:48:05 AM	Approver
	11-Nov-2020 12:39:36 PM	Approver
	11-Nov-2020 01:21:36 P	Author
	11-Nov-2020 02:27:30 PM	Approver