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Protocol for Study M19-850

Atopic Dermatitis: Open-Label Extension Study of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis

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ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EUDRACT:	2019-001227-12

FULL TITLE: A Phase 3b, open-label treatment extension study of upadacitinib for the treatment of adult subjects with moderate to severe atopic dermatitis who completed treatment in Study M16-046

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

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1 SYNOPSIS

Title: A Phase 3b, open-label treatment extension study of upadacitinib for the treatment of adult subjects with moderate to severe atopic dermatitis who completed treatment in Study M16-046	
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, Crohn's disease, ulcerative colitis, axial spondyloarthritis, 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. The results from the RA studies have been submitted for marketing authorization application. Upadacitinib is generally safe and well tolerated in the RA patient population. No new safety concerns have been identified in the ongoing studies for other indications.
Objective(s) and Endpoint(s):	The objective of this study is to assess the long-term safety, tolerability and efficacy of upadacitinib in adult subjects with moderate to severe atopic dermatitis who completed treatment in Study M16-046. The safety endpoints will serve as the primary endpoints in Study M19-850. Primary Safety Endpoints • Treatment emergent adverse events (TEAEs); • Serious adverse events (SAEs); • Adverse events of special interest (AESI); • AEs leading to discontinuation of study drug; • Vital signs, laboratory tests, and physical examination findings. Other Exploratory Endpoints The following efficacy endpoints will be assessed at all visits through Week 52. All endpoints are defined relative to the Baseline values in Study M16-046. • Change and percent Change from Baseline in EASI; • Change and percent change from Baseline in Worst Pruritus Numerical Rating Scale NRS; • Proportion of subjects achieving EASI 75/90/100; • Change from Baseline in body surface area (BSA);

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	• Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline among subjects who had Worst Pruritus NRS ≥ 4 at 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; • Proportion of subjects achieving 75% reduction in EASI in the head and neck body region among subjects who received dupilumab in Study M16-046 and did not achieve 75% reduction in EASI in the head and neck at Week 24 of Study M16-046; • Proportion of subjects achieving 75%/90%/100% reduction in EASI (EASI 75/90/100) among subjects who received dupilumab in Study M16-046 and did not achieve EASI 75 at Week 24 of Study M16-046; • Proportion of subjects achieving EASI 90/100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 90 at Week 24 of Study M16-046; • Proportion of subjects achieving EASI 100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 100 at Week 24 of Study M16-046; • Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS reduction ≥ 4 among subjects who had Worst Pruritus NRS ≥ 4 at Baseline, received dupilumab in Study M16-046 and did not achieve Worst Pruritus NRS reduction ≥ 4 at Week 24 of Study M16-046.
Investigator(s):	Multicenter; investigator information on file at AbbVie.
Study Site(s):	Up to 150 sites globally.
Study Population and Number of Subjects to be Enrolled:	Approximately 600 subjects who complete treatment in Study M16-046 and elect to enroll in this open label treatment extension study. The sample size is determined by the sample size of Study M16-046 and the consenting for the extension.
Investigational Plan:	This is a Phase 3b, open-label, single arm, treatment extension study.
Key Eligibility Criteria:	Demographics • Subjects should have successfully completed treatment in Study M16-046, without meeting any permanent discontinuation criteria. • Subject remains eligible to continue treatment in the long-term extension study by not meeting any of the criteria during Study M16-046 that would have warranted study drug discontinuation. Prior/Concomitant Therapy • Subjects should not be taking excluded concomitant medication during the end of treatment in Study M16-046, according to the Study M16-046 protocol.

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Study Drug and Duration of Treatment:	Upadacitinib 30 mg QD for a study treatment duration of 52 weeks.
Date of Protocol Synopsis:	07 January 2021

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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 2018 Consensus-based European guidelines for treatment of AD 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, 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 efficacious treatment of inflammatory and autoimmune disorders such as AD, rheumatoid arthritis (RA), psoriatic arthritis, Crohn's disease, ulcerative colitis, axial spondyloarthritis, 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%; $P = 0.032$ versus [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.

Upadacitinib is also being investigated in clinical programs for various indications including RA and inflammatory bowel disease. The results from the RA studies have been submitted for marketing authorization application. Upadacitinib is generally safe and well tolerated as demonstrated in the RA patient population. No new safety concerns have been identified in the ongoing studies for other indications. Upadacitinib is expected to be well tolerated in adult subjects with moderate to severe AD.

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Clinical Hypothesis

Based on the differentiated selectivity profile for JAK1 inhibition, upadacitinib could demonstrate a sustained, favorable benefit-risk profile in AD.

Additional information regarding indications under study can be found in the current edition of the upadacitinib Investigator's Brochure.[10]

2.2 Benefits and Risks to Subjects

Treatment of AD in 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, dyspigmentation, and striae. Common AEs associated with use of topical calcineurin inhibitors are transient warmth, burning, itching, or stinging at the application site. When topical therapies are insufficient for treating the signs and symptoms of AD, systemic therapy or phototherapy are generally added to topical agents.[4,11]

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.[5,12] 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.[5,12]

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)[13] and United States (US)[14] 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), 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.[13] Dupilumab is generally well-tolerated, and the most common AEs are injection site reaction, conjunctivitis, and blepharitis.[5,12]

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.[5,12] 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, or azathioprine.[5,12]

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.[5,12] The most common AEs associated with use of methotrexate are gastrointestinal disorders (e.g., stomatitis, oral ulcers, dyspepsia, abdominal pain, nausea, diarrhea) and abnormal liver function tests (e.g., increased

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aspartate transaminase [AST] or increased alanine transaminase [ALT]).[5,12] 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.[5,12]

Taken together, these agents may generally increase the risk of infections and cytopenias, gastrointestinal disorders, and may impact renal and/or liver function.[5,12] Rarely, lymphoproliferative disorders, lymphoma, and other malignancies are associated with these agents.[5,12]

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.[15,16]

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 also 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 (CPK); both increased and reduced hemoglobin, depending on baseline inflammatory burden; and reductions in white blood cell (WBC) 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 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.

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 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.

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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]

In view of the COVID-19 pandemic, the benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to assess the long-term safety, tolerability and efficacy of upadacitinib in adult subjects with moderate to severe AD who successfully completed treatment in Study M16-046.

3.2 Primary Safety Endpoints

- Treatment emergent adverse events (TEAEs);
- Serious adverse events (SAEs);
- Adverse events of special interest (AESI);
- AEs leading to discontinuation of study drug;
- Vital signs, laboratory tests, and physical examination findings.

3.3 Other Exploratory Endpoints

The following efficacy endpoints will be assessed at all visits through Week 52. Baseline refers to the Baseline value in Study M16-046. All endpoints are defined relative to the Baseline values in Study M16-046.

- Change and percent Change from Baseline in EASI;
- Change and percent change from Baseline in Worst Pruritus Numerical Rating Scale (NRS);
- Proportion of subjects achieving EASI 75/90/100;
- Change from Baseline in body surface area (BSA);
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from Baseline among subjects who had Worst Pruritus NRS ≥ 4 at 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;

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- Proportion of subjects achieving 75% reduction in EASI in the head and neck body region among subjects who received dupilumab in Study M16-046 and did not achieve 75% reduction in EASI in the head and neck body region at Week 24 of Study M16-046;
- Proportion of subjects achieving 75%/90%/100% reduction in EASI (EASI 75/90/100) among subjects who received dupilumab in Study M16-046 and did not achieve EASI 75 at Week 24 of Study M16-046;
- Proportion of subjects achieving EASI 90/100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 90 at Week 24 of Study M16-046;
- Proportion of subjects achieving EASI 100 among subjects who received dupilumab in Study M16-046 and did not achieve EASI 100 at Week 24 of Study M16-046;
- Proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS reduction ≥ 4 among subjects who had Worst Pruritus NRS ≥ 4 at Baseline, received dupilumab in Study M16-046 and did not achieve Worst Pruritus NRS reduction ≥ 4 at Week 24 of Study M16-046.

3.4 Biomarker Samples

Optional biospecimens (e.g., blood, serum, plasma, and skin biopsies) will be collected at specified time points through Week 52 to evaluate known and/or novel disease-related or drug-related biomarkers. Optional lesional and non-lesional skin biopsies will be collected at Baseline and Week 16. Further, optional deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and serum/plasma samples will be collected at Week 4, Week 16, and Week 52.

Of note, 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, tyrosine kinase 2 [Tyk2], tumor necrosis factor [TNF]), or other genes believed to be related to AD and other inflammatory diseases (Filaggrin [FLG], Claudin 1, Human Leukocyte Antigen [HLA], Immunoglobulin E [IgE]). 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.

This research may be exploratory in nature and the results may not be included with the clinical study report.

3.5 Safety Evaluations

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

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4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b, single arm, open-label extension (OLE) study for adults (18 – 75 years of age at entry into Study M16-046) with moderate to severe AD who have successfully completed treatment in Study M16-046. These subjects should be determined to be eligible to continue treatment with upadacitinib by the Principal Investigator during the Baseline visit of this OLE study. The Baseline visit for this study will be the Week 24 visit of Study M16-046.

The study is comprised of a Baseline visit (Week 24 visit of Study M16-046), a 52-week open-label treatment period, and an End-of-Study Follow-Up Visit (or phone call if a visit is not possible) 30 days after the last dose of upadacitinib. The 30-day follow-up visit is done to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs is required. These subjects will be considered as having completed the study.

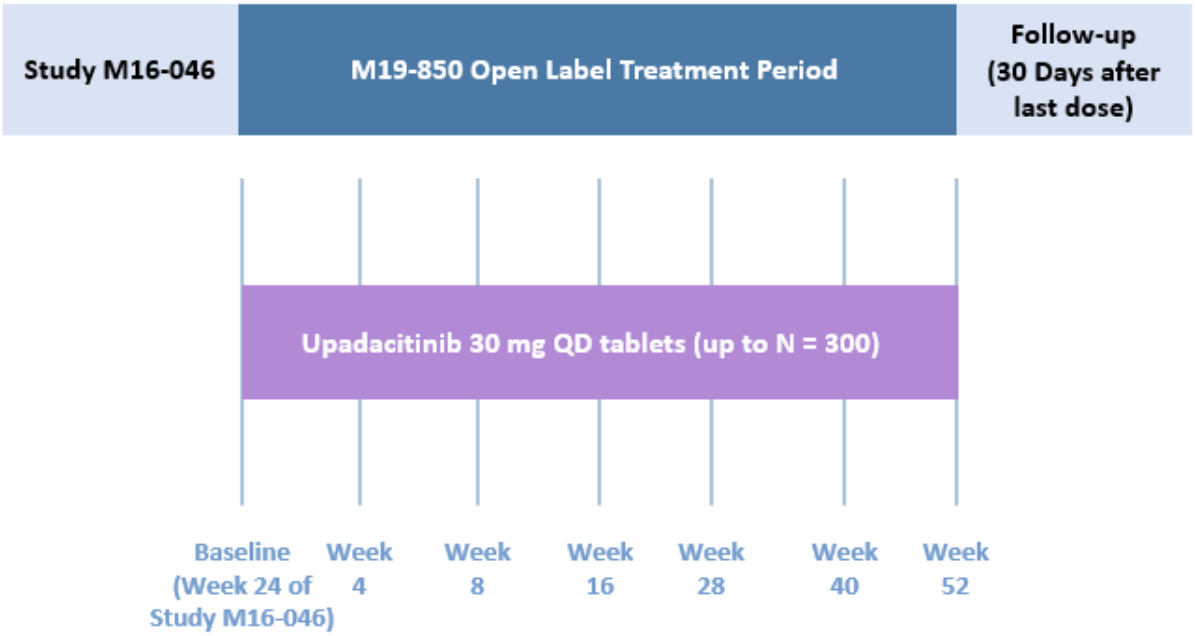
Subjects, who are eligible to enroll in the OLE study, will receive daily oral doses of upadacitinib 30 mg from the Baseline visit up to the Week 52 visit.

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

See Section 5 for information regarding eligibility criteria.

An interim analysis will occur after all ongoing subjects have completed the Week 16 visit.

Figure 1. Study Schematic



QD = once daily

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4.2 Discussion of Study Design

Appropriateness of Measurements

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

Suitability of Subject Population

Subjects who have completed Study M16-046 without permanent discontinuation of study drug are eligible for Study M19-850. 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 this OLE study.

Selection of Doses in the Study

This study will evaluate upadacitinib (30 mg QD) as the same dose selected in Study M16-046. 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 Phase 2 AD Study M16-048, which evaluated 3 doses of upadacitinib (7.5 mg, 15 mg, or 30 mg QD) versus placebo. In addition, all the currently available PK, pharmacodynamic, safety, and efficacy data from upadacitinib studies were used to support the selection of these doses.

The Phase 2 study results demonstrated superior efficacy of upadacitinib with an acceptable safety profile at the selected dose (30 mg QD) compared to placebo in subjects with moderate to severe AD. 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 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.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all 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. Subjects should have successfully completed treatment in Study M16-046, without developing any permanent discontinuation criteria.
- 2. Subject 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 study-specific procedures and comply with the requirements of this study protocol.

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- 3. Subject remains eligible to continue treatment in the long-term extension study by not meeting any of the criteria during Study M16-046 that would have warranted study drug discontinuation:
  - a) Rescue treatment was administered outside of the protocol-specified parameters in Study M16-046;
  - b) Initiation of any systemic rescue therapy for AD as defined in Study M16-046;
  - c) Any subject with an EASI score worsening of 25% or more compared with their Study M16-046 Baseline EASI score at any 2 consecutive scheduled study visits (after a trial of rescue treatment, if appropriate);
  - d) Anaphylactic reaction or other severe systemic or local reaction to study drug injection;
  - e) Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug;
  - f) The investigator believes it is in the best interest of the subject;
  - g) The subject requests withdrawal from the study;
  - h) Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk;
  - i) Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk;
  - j) Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study;
  - k) The subject becomes pregnant or plans to become pregnant while on study drug;
  - l) Malignancy, except for localized non-melanoma skin cancer (NMSC) or carcinoma in-situ of the cervix;
  - m) Subject develops a GI perforation;
  - n) 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;
  - o) 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.

Contraception

- 4. Females of childbearing potential must not have a positive urine pregnancy test at the Baseline Visit prior to study drug dosing.
- 5. If female, subject must be postmenopausal OR permanently surgically sterile OR for females of childbearing potential practicing at least one protocol-specified method of birth control (refer to Section 5.2), that is effective from the Baseline Visit through at least 30 days after the last dose of study drug.

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- 6. Female subject must not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of the study drug.
- 7. Additional local requirements may apply (see Section 5.2).

Prior and Concomitant Therapy

- 8. Subjects should not be taking excluded concomitant medication at the end of treatment in Study M16-046, according to the M16-046 protocol.

Medical History

- 9. Any ongoing adverse event from Study M16-046 or medical condition prior to continuing in the long-term extension study which would put the subject at risk by participating in the open label treatment extension study.

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 30 days after the last dose of study drug. Females must commit to one of the following methods of highly effective birth control:
  - Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation.
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).

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- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner (the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence (unless not acceptable per local practices), defined as: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Baseline.
- 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

Concomitant oral and topical exposure to any other JAK inhibitors (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

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- certolizumab
- dupilumab
- efalizumab
- etanercept
- golimumab
- guselkumab
- infliximab
- ixekizumab
- natalizumab
- omalizumab
- risankizumab
- 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:

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

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

Corticosteroids

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

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

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

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Investigational Drugs

Investigational drugs are 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 are not allowed during the study. Tanning booth use or extended sun exposure that could affect disease severity or interfere with disease assessments are not allowed 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 Section 5.4 Rescue Therapy). 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.

Topical anti-infectives, topical antihistamines, and bleach baths 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 Medical Director (TA MD).

Vaccines

Live vaccinations are prohibited during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.

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 (Bacilli Calmette-Guérin);
- Typhoid (oral).

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

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Cannabis

Use of medicinal and recreational marijuana is prohibited during the study.

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.

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong cytochrome P450 3A isoform subfamily (CYP3A) inhibitors or strong CYP3A inducers is not allowed 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.

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If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. See Section 5.8 Study Drug Administration 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 the Baseline visit 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 AD since date of diagnosis (based on subject recollection and available medical records) should be reviewed.

If there are any questions regarding concomitant or prior therapies, the AbbVie TA MD should be contacted.

Required Concomitant Medications

Twice daily use of an additive-free, bland emollient that was used during Study M16-046 should be continued for the duration of Study M19-850.

Note: Subject may use prescription moisturizers or moisturizers containing ceramide, urea, filaggrin degradation products or hyaluronic acid if such moisturizers were initiated before Study M16-046 Baseline 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.

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

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 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, lack of

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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, electrocardiogram (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 Study M19-850 baseline for any subject with an EASI score worsening of 25% or more compared with their Study M16-046 Baseline EASI score at any 2 consecutive scheduled study visits in this study (after a trial of rescue treatment, if appropriate; see Section 5.4 Rescue Therapy). For example, permanent study drug discontinuation would apply at Week 4 if EASI score worsening criteria are met at Study M19-850 Baseline and Week 4 without rescue therapy given at Study M19-850 Baseline. Permanent study drug discontinuation would apply at Week 8 if EASI score worsening criteria are met at Week 4 and Week 8 with rescue therapy given at Study M19-850 Baseline. This rule applies similarly to later timepoints.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator and the AbbVie Therapeutic Area Medical/Scientific Director.
- 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 enrollment of the subject in the study, when continuation of the study drug would place the subject at risk as determined by the AbbVie Therapeutic Area Medical/Scientific Director.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie Therapeutic Area Medical/Scientific Director.
- Subject is non-compliant with tuberculosis (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 non-melanoma skin cancer (NMSC) or carcinoma in-situ of the cervix.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial in consultation with the AbbVie Therapeutic Area Medical/Scientific Director.
- Subject develops a GI perforation (defined as acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention other than appendicitis or mechanical injury). See also Section 6.2 Toxicity Management.

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- 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 final status of the subject. At a minimum, 2 telephone calls must be made and one certified letter must be sent and documented in the subject's source documentation.

COVID-19 Pandemic-Related Acceptable Protocol Modification

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

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

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

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

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

5.6 Follow-Up for Subject Withdrawal from Study

Discontinuation of Study Drug and Study Participation

Subjects who prematurely discontinue study drug treatment will be discontinued from study participation entirely. If the subject is prematurely discontinued from the study, a Premature Discontinuation (PD visit) should be completed as soon as possible, preferably within 2 weeks or 12 weeks after last injection from Study M16-046, whichever is sooner. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment.

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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 or 12 weeks after last injection from Study M16-046, whichever is sooner. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/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 Treatment After End of Study

At the subject's last visit, the investigator will discuss the appropriate subsequent treatment with the subject. AbbVie will not provide drug or any other therapy once the subject's participation is concluded.

5.8 Study Drug

The study drug information is presented in Table 2.

Table 2. Description of Study Drug

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Upadacitinib (ABT-494) tablet	oral	Film-coated tablet	30 mg	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.

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

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

Storage and Disposition of Study Drug

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

The investigational product is for investigational use only and are to be used only within the context of this OLE study. The investigational product 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.

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Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via 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 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.

Dispense Study Drug

The type and amount of kits dispensed will be managed by the IRT. Upadacitinib tablets will be dispensed through IRT beginning at Baseline (Day 1) according to dispensation schedule 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 dispensed by the site. Accountability will also need to be recorded in the IRT system at each visit.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

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

- DTP shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
- Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of PROs). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; this may be provided by the courier after delivery if social distancing measures are in place. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

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

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State of Emergency or Pandemic-Related Acceptable Protocol Modifications for Home Healthcare Services

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

The investigator should be available via phone call if a consultation is necessary.

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

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

Individuals performing home visits need to be added to the delegation log.

Study Drug Administration

Upadacitinib 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 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 tablets should be swallowed whole and should not be split, crushed, or dissolved.

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.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible

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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 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.

In cases of state of emergency or pandemic situations, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

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. AEs or SAEs ongoing at Week 24 of Study M16-046 will be followed in Study M19-850. 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.

Subjects will complete the following questionnaires (described below) as specified in the Operations Manual (Appendix F): Worst Pruritus NRS; and Head and Neck - Patient Global Impression of Severity

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(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 AEs or any review of laboratory findings.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

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

Subjects will complete the following questionnaires as specified in the schedule of assessments:

Worst Pruritus NRS

The Worst Pruritus Numerical Rating Scale (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 NRS will be administered on the tablet at specified site visits in Appendix D.

Head and Neck Patient Global Impression of Severity

The Head and Neck - Patient Global Impression of Severity (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 PGIS will be administered on the tablet at specified site visits in Appendix D.

Investigator Assessment

The investigator assessments will be recorded on paper worksheets and entered into the eCRF and conducted at the study visits specified in Appendix D. In order to minimize variability, the same assessor should evaluate the subject at each visit for the duration of the trial. 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 principal investigator to ensure that all assessors are qualified and trained to perform assessments and that all training is documented.

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Eczema Area and Severity Index

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 physician 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.

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

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.

Subjects with a negative TB test result during Study M16-046 will require an annual TB follow-up test to be performed. At Week 28 (approximately 1 year after the TB screening in Study M16-046), all subjects will be assessed for evidence of increased risk for TB by a risk questionnaire (see Operations Manual, Appendix F) and tested for TB infection by QuantiFERON-TB Gold test. The site staff will complete the TB risk questionnaire in its entirety and enter the data into the appropriate eCRF. One or more "yes" response on the TB risk questionnaire indicates increased risk of TB.

The annual TB-test can be completed at the earliest feasible opportunity if not able to be completed per protocol schedule due to COVID-19 restrictions. If an annual TB test (at Week 28) is newly positive (seroconversion), a chest x-ray needs to be performed as soon as possible to aid in distinguishing active versus latent TB. Any positive TB test during 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 at Week 28 visit, the case (including the TB test results) should be discussed with the AbbVie TA MD.

Subjects with evidence of active TB must not continue in the OLE study.

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TB Testing:

- The QuantiFERON-TB Gold test (or equivalent) should be performed for all subjects. The purified protein derivative (tuberculin) (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 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.
- If only a PPD is placed at Study M16-046, then the TB test to be used for the open label study for that subject is the PPD test. 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 in the TB questionnaire) 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 (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold.

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Tuberculosis Prophylaxis

Note: Rifampicin and Rifapentine are not allowed for TB prophylaxis.

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.

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.

Chest X-Ray

Chest x-ray (posterior-anterior and lateral views) is required for all subjects to rule out the presence of TB or other clinically relevant findings following a newly positive result of a TB test.

Subjects can have a repeat chest x-ray at any time during the study as warranted based on the opinion of the investigator.

A radiologist or pulmonologist must perform and document an assessment of the chest x-ray. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the chest x-ray, the Principal Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the chest x-ray demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator should contact the AbbVie TA MD.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

In the event that CXR may not be performed at the planned timepoint due to a state of emergency or pandemic situation, perform the CXR at the next feasible visit.

12-Lead Electrocardiogram

A 12-lead ECG will be performed at Week 28 (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

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State of Emergency or Pandemic-Related Acceptable Protocol Modifications

In the event that ECG may not be performed at the planned timepoint due to a state of emergency or pandemic situation, perform the 12-lead ECG at the next feasible visit.

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 AD 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.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to a state of emergency or pandemic situation, subject visits may be conducted via phone or video conference. In these situations, height and weight measurements may be performed by the subject or caregiver as needed.

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.[17]

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to a state of emergency or pandemic situation, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

Physical Examination

A complete physical examination including whole surface and adjacent mucosal surfaces for potential NMSC will be performed at visits specified in Appendix D. 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.

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State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Due to a state of emergency or pandemic situation, subject visits may be conducted via phone or video conference. In these situations, if a visit by phone or video conference occurs at one of the designated study visits specified for complete physical examination, the complete physical examination will be performed at the next feasible visit.

Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests listed in Table 3. Blood and urine samples will be collected following a minimum 8-hour fast. If a subject is not able to fast when necessary, 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 Baseline laboratory test results for clinical assessment for a particular test will be defined as the Week 24 values from Study M16-046 prior to the initial dose of study drug in Study M19-850.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

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

If laboratory samples cannot be obtained, study drug administration may be continued provided the subject has at least 1 post-baseline visit and investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current laboratory values. Laboratory draws should be obtained as close as possible to the scheduled visit.

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Table 3. Clinical Laboratory Tests

Clinical Laboratory Tests		
Hematology	**Clinical Chemistry**	**Other Tests**
Hematocrit Hemoglobin RBC count WBC count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count	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	<u>Central Lab Tests:</u> Serum pregnancy (beta human chorionic gonadotropin [bHCG]) test Hepatitis B virus deoxyribonucleic acid polymerase chain reaction (HBV DNA PCR [Per Toxicity Management Guidelines only]) QuantiFERON-TB Gold High-sensitivity C-reactive protein (hsCRP) <u>Local Lab Tests:</u> Urine pregnancy test PPD test / T-SPOT TB
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocytes Nitrites Microscopic examination, if needed		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; CPK =creatine phosphokinase; DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HDL-C = high-density lipoprotein cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; PCR = polymerase chain reaction; PPD = purified protein derivative (tuberculin); RBC = red blood cell; TB = tuberculosis; WBC = white blood cell

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

Pregnancy Tests (Serum and Urine)

A urine pregnancy test will be performed for female of childbearing potential at the Baseline Visit (Week 24 visit of Study M16-046) and at minimum at monthly intervals if not already done at study visits. More frequent pregnancy tests will be performed throughout the study if required per local requirements. If the interval between the study visits is more 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 urine pregnancy test performed at the site or at home is negative, then dosing with study drug may continue.
- In case of positive urine pregnancy test, a serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is negative, study drug may continue. If the positive urine pregnancy test is confirmed with the serum pregnancy test the subject is not considered eligible to continue in the OLE study and study drug must be permanently

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discontinued. 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 not eligible;
- Negative, the subject can be enrolled into the study;
- Still borderline ≥ 3 days later, the subject is considered not eligible.

If during the course of the study a female becomes surgically sterile or post-menopausal and complete documentation as described in Section 5.2 for female is available, pregnancy testing is no longer required.

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

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. In contrast, an adverse reaction (AR) refers to all untoward and unintended responses to an investigational medicinal product at least possibly related to any dose administered.

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Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study drug, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.2 regarding toxicity management) and/or if the investigator considers them to be AEs.

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

If any of the following events are reported, then the following supplemental report must be completed (Table 4).

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Table 4. Supplemental Electronic Case Report Forms

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

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eCRF = electronic case report form; ULN = upper limit of normal

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE. Any SAE that has been determined to be at least possibly related to the study drug is defined as a serious AR.

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

All AEs reported from the time of study drug administration through 30 days after the last dose of study drug administration will be collected, whether solicited or spontaneously reported by the subject.

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

Adverse event information will be collected as shown in Figure 2.

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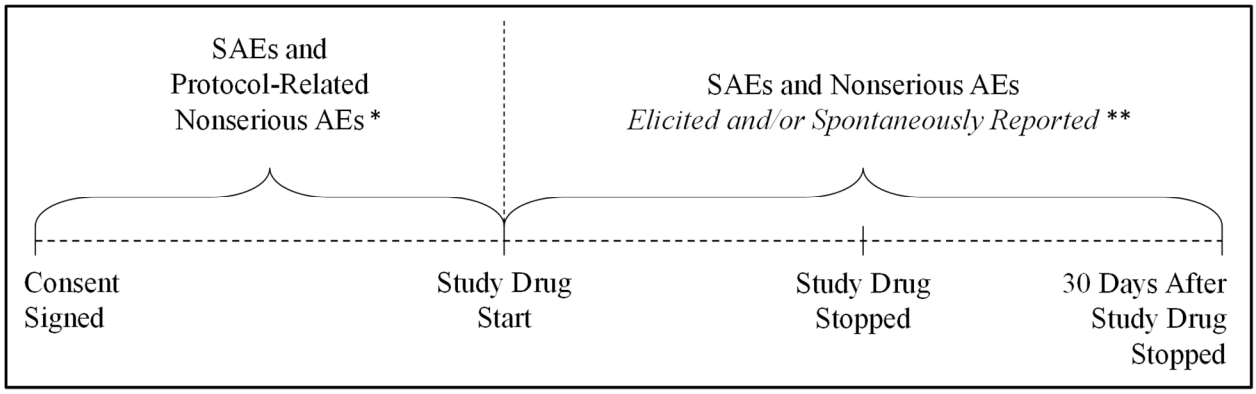
Figure 2. Adverse Event Collection



* Any AEs occurring prior to the first dose of Study M19-850 should be considered as AEs for Study M16-046, regardless of when the consent form is signed.

** Any AEs occurring on or after the first dose of Study M19-850 should be considered as AEs for Study M19-850.

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. A SUSAR is an adverse reaction of which the nature or severity is not consistent with the applicable product information such as investigator's brochure.

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 AESI 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
- Renal dysfunction
- Hepatic disorders
- Elevated CPK

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- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system).
- COVID-19 (consider while pandemic is ongoing).

Adverse Event Severity and Relationship to Study Drug

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

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

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Severe (Grade 3 - 5)	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (Self care ADL 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.

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Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy will be collected from the date of the first dose through 30 days following the last dose of study drug. The pregnancy outcome will be followed.

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.

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 TEAEs (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days after the last dose of study drug will be tabulated by primary MedDRA System Organ Class [SOC] and preferred term [PT]). The tabulation of the number of subjects with TEAEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA PT 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. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

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

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team Dept. [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Office: +1 (847) 938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

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

Contact Information:

Office: [redacted]
Mobile: [redacted]
Email: [redacted]

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

HOTLINE: +1 (973) 784-6402

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

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

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

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

6.2 Toxicity Management

The toxicity management of AEs, including AESI consists of safety monitoring (review of AEs on an ongoing basis, and periodical/ad hoc review of safety issues, interruption of study drug dosing with

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appropriate clinical management if applicable, and discontinuation of the subjects from the study drug). The management of specific AEs and laboratory parameters is described below.

Management of Serious Infections

Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug. If a subject develops zoster, or shows infection with or reactivation of any other herpes virus (e.g., HSV, VZV, EBV, CMV), any study drug should at least be temporarily interrupted until the episode resolves, or discontinued as patient safety requires.

Management of Herpes Zoster

If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves. Serious AEs of herpes zoster should be reported as serious infections.

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. Subjects with acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention (except for appendicitis or mechanical injury) must be permanently discontinued from study drug.

Management of Thrombosis Events

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

Management of Malignancy

Subjects who develop malignancy other than NMSC or carcinoma in-situ of the cervix must be discontinued from the study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at increased risk of 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.

COVID-19

Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The COVID-19 eCRF must be completed.

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Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 5, and may require a supplemental eCRF to be completed (see Protocol Section 6.1 [Complaints and AEs]). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 5, the repeat testing must occur as soon as possible.

Table 5. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample • If hemoglobin decreases ≥ 3.0 g/dL from Baseline, without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline and an alternative etiology is known or the hemoglobin value remains in the normal reference range, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its Baseline value.
Absolute neutrophil count (ANC)	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Interrupt study drug if confirmed < 500/µL by repeat testing with new sample. If value returns to normal reference range or its Baseline value, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason that rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.
Absolute lymphocyte counts (ALC)	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total white blood cell count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its Baseline value.
Platelet count	• If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its Baseline value.
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

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Laboratory Parameter	Toxicity Management Guideline

	quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from baseline).
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD.
	• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Study M16-046 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.
	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.

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

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6.3 Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular and thromboembolic AEs in a blinded manner. Briefly, CAC consists of 11 voting members including 5 cardiologists, 3 neurologists and 3 thrombotics/vascular specialists. The events that are adjudicated are defined in the CAC charter. The Sponsor/CRO will provide the list of events based on the pre-specified search criteria and all relevant information as a case package for CAC adjudication on a monthly basis. Each randomly assigned CAC member will conduct independent review and submit an assessment of the adjudication outcome. Events may be re-adjudicated if clinically relevant data changes or updates occur. If a decision is not reached via independent review for events, a panel meeting may be held for the purpose of adjudication. A CRO is responsible for coordinating all adjudication activities. The details of the composition and process for the CAC are provided in the CAC Charter.

6.4 Other Safety Data Collection

Specific manifestations of AD (i.e., itching, excoriations, oozing, crusting, erythema, etc.) should not be reported as individual AEs if they are considered to be a worsening of the underlying disease; instead, worsening of AD should be reported as 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 statistical methods provided in this protocol will be focused on efficacy and safety summaries. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP), which will be signed off within 30 business days after the first subject is dosed. Furthermore, a Week 16 Interim Analysis will be conducted after all ongoing subjects have completed Week 16 and all data pertaining to Week 16 are cleaned. 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 subjects who receive at least one dose of study drug in the study and will be used for the efficacy analyses.

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The Safety Population is the same as the ITT Population for this study. This population will be used to provide a comprehensive summary of safety.

7.3 Statistical Analyses for Efficacy

All efficacy endpoints will be summarized in the ITT population.

The ITT Population will be summarized by treatment group as randomized at the Baseline of Study M16-046.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, maximum, as well as the 95% confidence intervals (CIs) of the mean values. Categorical variables will be summarized by counts and percentages, as well as the 95% CIs of the percentages.

There will be no statistical testing for all of the efficacy and safety endpoints.

Efficacy assessments will be summarized by Observed Cases (OC) approach. No data imputation will be applied. Observed Cases will not include values after a subject prematurely discontinue from study drug.

Sample Size Estimation

Approximately 600 subjects that complete treatment in Study M16-046 will roll over in this open label treatment extension study. The sample size is determined by the completion of Study M16-046 and the consenting for the extension.

7.4 Statistical Analyses for Safety

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 the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as those that began or worsened in severity after the first dose of study drug and no more than 30 days after the last dose of the study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA SOC and 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 AESI will be provided as well.

For laboratory and vital signs, mean change from Study M16-046 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 biomarker data for the purpose of identification of prognostic, predictive, surrogate, and pharmacodynamic biomarkers associated with efficacy or safety. The

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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

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Independent Ethics Committee/Institutional Review Board (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.

In cases of state of emergency or pandemic situations leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to the Operations Manual for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

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

In cases of state of emergency or pandemic situations, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original,

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accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

Electronic Patient Reported Data

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

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health. Worst Pruritus NRS will be completed electronically via an onsite tablet device. 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.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AD	atopic dermatitis
AE	adverse event
AESI	adverse events of special interest
BCG	bacilli Calmette-Guérin
BSA	body surface area
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CLDN1	Claudin 1
CNS	central nervous system
COVID-19	Coronavirus Disease – 2019
CPK	creatine phosphokinase
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450 3A isoform subfamily
DNA	deoxyribonucleic acid
DTP	Direct-to-patient
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ePRO	Electronic Patient Reported Outcome
EU	European Union
EudraCT	European Clinical Trials Database
FLG	Filaggrin
FSH	follicle-stimulating hormone
GCP	Good clinical practice
GI	gastrointestinal
HLA	Human Leukocyte Antigen
HN-PGIS	Head and Neck - Patient Global Impression of Severity
hs-CRP	High-sensitivity C reactive protein
ICH	International Council for Harmonisation

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IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IGRA	Interferon Gamma Release Assay
IL	interleukin
IMP	Investigational Medicinal Product
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
JAK1	Janus kinase 1
JAK2	Janus kinase 2
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NK	natural killer
NMSC	non-melanoma skin cancer
NRS	numerical rating scale
OC	Observed Cases
OLE	open-label extension
PD visit	Premature Discontinuation visit
PK	Pharmacokinetic(s)
PPD	purified protein derivative (tuberculin)
PRO	patient-reported outcome
Ps	psoriasis
PT	preferred term
PUVA	psoralen and ultraviolet A radiation
QD	once a day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula

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RA	rheumatoid arthritis
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	system organ class
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
Tyk2	tyrosine kinase 2
US	United States
UV	ultraviolet
WBC	white blood cell

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-850: Evaluation of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 07 January 2021

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

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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
		Data and Statistical Sciences
		Pharmacovigilance & Patient Safety
		Immunology Translational Science
		Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The individual activities are described in detail in the **Operations Manual** (Appendix F). Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Study Activities Table

Activity *The activities performed at the Week 24 visit of Study M16-046 will be considered the Baseline activity for Study M19-850 (activities with blue checkmarks in Baseline column only).*	Baseline	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52	Unscheduled Visit	PD Visit	30 Days After Last Dose
Visit Window (days)		± 3	± 3	± 3	± 7	± 7	± 7			± 3
INTERVIEWS & QUESTIONNAIRES										
Informed consent	✓									
Eligibility criteria	✓									
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk factor questionnaire (annually after last assessment in Study M16-046)					✓					
Review pregnancy avoidance recommendations (females of childbearing potential only)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PROS										
Worst Pruritus NRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	
HN-PGIS	✓	✓		✓						
LOCAL LABS & EXAMS										
Body Weight	✓	✓		✓		✓				
Vital Signs (at FU if needed to monitor AEs)	✓	✓		✓		✓				✓
Physical Exam (at follow-up if needed to monitor AEs)	✓									✓
Investigator Assessment (EASI, BSA)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Chest x-ray (annually after last assessment in Study M16-046 if newly positive TB results)					✓					
12-Lead ECG					✓					

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Activity *The activities performed at the Week 24 visit of Study M16-046 will be considered the Baseline activity for Study M19-850 (activities with blue checkmarks in Baseline column only).*	Baseline	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52	Unscheduled Visit	PD Visit	30 Days After Last Dose
Visit Window (days)		± 3	± 3	± 3	± 7	± 7	± 7			± 3
Urine pregnancy test for all female subjects of childbearing age. Monthly home urine pregnancy testing will be performed for visits with > 1 month interval. In case of a positive urine pregnancy test a serum pregnancy test will be performed.	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CENTRAL LABS										
Clinical chemistry, hematology, urinalysis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓(only as needed for AEs)
hsCRP	✓	✓	✓				✓	✓	✓	
QuantiFERON-TB Gold test (and/or local PPD skin test)					✓					
Total serum Immunoglobulin E (IgE)	✓	✓		✓			✓			
Optional Biomarker Sample: Skin biopsy (lesional/non-lesional)	✓			✓						
Optional Biomarker Sample: Whole blood (DNA/RNA/Serum/Plasma)	✓	✓		✓			✓			
TREATMENT										
Dispense study drug (excluding Week 52)	✓		✓	✓	✓	✓				

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APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	28 May 2019
Version 1.1 (VHP countries only)	26 July 2019
Version 2.0	26 August 2019
Version 3.0	28 January 2020
Version 3.1 (Germany and Czech Republic only)	02 April 2020
Version 4.0	06 March 2020
Version 4.1 (Germany and Czech Republic only)	10 June 2020
Version 4.1.1 (Germany only)	31 July 2020

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

Summary of Protocol Changes:

The purpose of this version is to incorporate necessary protocol modifications due to the COVID-19 pandemic, add an interim analysis, incorporate additional description about management of gastrointestinal performation and serious herpes zoster, and provide clarification about the timing of efficacy assessments.

Protocol modifications due to the COVID-19 pandemic are as follows:

- Section 2.2 – included information on the re-evaluation of the benefit and risk to subjects participating in the study. There is no additional risk to subjects or state what the additional risks are that may change the benefit-risk balance to participating subjects.
- Section 5.5 – added instructions to refer to Operations Manual for necessary changes to activities or procedures in the event of temporary study [drug] interruption/halt.
- Section 5.7 – included instructions that in the event the subject cannot pick up study drug onsite, refer to the Operations Manual for DTP shipment as needed and permitted by local regulations.
- Section 5.9 – clarified that protocol deviations may include modifications due to COVID-19.
- Section 8.2 – noted that AbbVie will modify the study protocol as necessary due to the pandemic, referring to the Operations Manual in Appendix F for additional details. Investigators must also notify AbbVie if any urgent safety measures are taken.
- Section 9 – noted that remote monitoring may be employed as needed
- Appendix D – added reference to Operations Manual for allowed modification

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- Appendix F – Operations Manual updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic.

Statements about the interim analysis were added to the following subsections to incorporate this change:

- Section 4.1 – Sentence added that an interim analysis will be performed after all subjects have completed the Week 16 visit.
- Section 7.1 – Sentence added that an interim analysis will be performed after all subjects have completed the Week 16 visit and all data pertaining to Week 16 are cleaned.

  Rationale: To assess efficacy and safety after switching from dupilumab to upadacitinib at a similar timeframe as the upadacitinib atopic dermatitis pivotal Phase 3 studies.

Updates to the description and management of gastrointestinal perforation (added text underlined) were made to:

- Section 5.5 – "Subject develops a gastrointestinal perforation (<u>defined as acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention</u> other than appendicitis or mechanical injury). See also Section 6.2 Toxicity Management."
- Section 6.2 – 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. Subjects with <u>acute, spontaneous perforation of the gastrointestinal tract that requires inpatient medical care or urgent surgical intervention (except for appendicitis or mechanical injury)</u> must be <u>permanently</u> discontinued from study drug.

  Rationale: To provide further clarity on the characteristics of GI perforations for investigators and requirement for permanent discontinuation of study drug.

Other changes:

- Synopsis and Section 3.3 – Wording was updated to state that efficacy endpoints will be assessed at all visits through Week 52 only.

  Rationale: To provide clarification about the timing of efficacy assessments.
- Section 6.2 – Wording about management of herpes zoster was added: "Serious AEs of herpes zoster should be reported as serious infections."

  Rationale: To incorporate wording from protocol version 4.1.1.
- Section 6.2 – Management of Hypersensitivity was removed. Management of hypersensitivity was included in Study M16-046 for subjects who received dupilumab and is not used in studies in which upadacitinib is the only treatment drug. No subjects receive dupulimab in this extension study.

  Rationale: Management of hypersensitivity is not needed in studies when upadacitinib is the only treatment drug.

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