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Protocol for Study M16-813

Indication: Risankizumab Versus Placebo for Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis

VERSION:	5.0	DATE:	13 October 2020
SPONSOR:	AbbVie	NUMBER OF SITES:	75 (planned)
ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab, ABBV-066	EUDRACT:	NA

FULL TITLE: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Risankizumab in Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis

Incorporating Versions 1.0, 2.0, 3.0, 4.0, and 5.0 and Administrative Change 1

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1 SYNOPSIS

Title: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Risankizumab in Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis	
Background and Rationale:	Atopic dermatitis (AD) is one of the most common chronic skin diseases, characterized by pruritus, erythema, edema, xerosis, erosions/excoriations, oozing, crusting, and lichenification. Interleukin (IL)-23, the target of risankizumab, was identified as one of the immune mediators shown to contribute to AD inflammation, and it may be involved in the pathogenesis of the disease phenotype. This study will provide data on the safety and efficacy of risankizumab as treatment for subjects with moderate to severe AD. The primary hypothesis for the study is that risankizumab will provide superior efficacy compared to placebo and will be well tolerated in subjects with moderate to severe AD.
Objective(s) and Endpoint(s):	The primary objective of this study is to assess the safety and efficacy of risankizumab for the treatment of moderate to severe AD in adult and adolescent subjects. **Primary Endpoint** The primary endpoint is the proportion of subjects achieving at least a 75% reduction from Baseline in Eczema Area and Severity Index (EASI 75) at Week 16. **Secondary Endpoints** Key secondary endpoints include the proportion of subjects achieving validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD) of "0" or "1" (on a 5-point scale) with a reduction from Baseline of ≥ 2 points at Week 16, and the proportion of subjects achieving a reduction of ≥ 4 points in worst pruritus numerical rating scale (NRS) from Baseline to Week 16. Other efficacy endpoints include change from Baseline in worst pruritus NRS, change in affected body surface area (BSA), and proportion of subjects achieving multiple levels of EASI and vIGA-AD responses at specified visits. Improvement in other patient-reported outcomes (PROs) will also be assessed. **Safety Endpoints** Safety evaluations include adverse event (AE) monitoring, vital sign measurements, electrocardiogram (ECG) variables, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration. **Pharmacokinetic and Immunogenicity Endpoints** Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (nAb) will be determined. Serum risankizumab concentrations will be summarized at each sampling time point for each dose group using descriptive statistics. ADA titers will be tabulated for each subject at the respective study visits. The number and percentage of subjects with ADA and nAb will be calculated by dose group.
Investigator(s):	Multi-center

Study Site(s):	The current assumption is to include up to 75 sites in the United States, Canada, Japan, and Australia. Depending on operational aspects, the number, allocation, and location of sites may be modified.
Study Population and Number of Subjects to be Enrolled:	Approximately 155 adult and adolescent subjects who have moderate to severe AD and meet the study's eligibility criteria will be randomized for participation in this study. The study plans to enroll approximately 20% of subjects from sites in Japan.
Investigational Plan:	This is a Phase 2, randomized, double-blind, placebo-controlled multicenter study to evaluate the safety and efficacy of risankizumab for the treatment of moderate to severe AD in adult and adolescent subjects with onset of symptoms at least 2 years before the Baseline Visit. The duration of the study will be up to 65 weeks and will include a screening period of up to 35 days, a 16-week double-blind treatment period (Period A), and a 36-week double-blind treatment period (Period B). The primary analysis will be performed when all subjects have completed Week 16. Eligible subjects will be randomized at Baseline to receive risankizumab 150 mg, risankizumab 300 mg, or matching placebo (2:2:1, respectively) at Week 0 and Week 4 of Period A. In Period B, subjects in the placebo group will be re-randomized in a 1:1 ratio to receive either risankizumab 150 mg or 300 mg for the remainder of the study. Subjects originally randomized to risankizumab 150 mg or 300 mg in Period A will stay on their previously-assigned treatment through the end of the study. All subjects will receive risankizumab at the Week 16, Week 28, and Week 40 visits. The last visit to the study site will occur at Week 52. Subjects will have a final follow up call 20 weeks after the last dose administration. During Period B, subjects with < EASI 50 response, as compared to Baseline, at the most recent prior and current scheduled visits will be allowed to begin approved concomitant rescue treatment after the assessments at the Week 24 visit and at any visit thereafter. Rescue treatment is limited to up to twice-daily application of topical corticosteroids.
Key Eligibility Criteria:	Eligible subjects will be adults who are ≥ 18 years old and, where locally permissible and approved, adolescent subjects who are at least 12 years old. Subjects must have a diagnosis of AD with onset of symptoms at least 2 years prior to Baseline. Subjects must have moderate to severe AD at the Baseline Visit, defined by EASI ≥ 16, BSA ≥ 10%, and vIGA-AD score of ≥ 3. Subjects must have a history of inadequate response to previous topical corticosteroid and/or topical calcineurin inhibitor treatments or a medical inability to receive these treatments. Subjects with prior exposure to any biologic immunomodulatory agent or Janus kinase (JAK) inhibitor will be excluded from the study. Concurrent treatment with systemic therapy for AD (biologic or non-biologic), as well as use of topical and/or phototherapy treatments, is prohibited throughout the study.

Study Drug and Duration of Treatment:	Period A (Baseline up to Week 16) Study site staff will administer study drug (risankizumab 150 mg, risankizumab 300 mg, or matching placebo) subcutaneously at the Baseline and Week 4 visits. Period B (Week 16 up through Week 52) Study site staff will administer either a risankizumab 150 mg or risankizumab 300 mg dose subcutaneously at the Week 16, 28, and 40 visits.
Date of Protocol Synopsis:	13 October 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

This study will provide data comparing risankizumab versus placebo for the treatment of adult and adolescent subjects with moderate to severe atopic dermatitis (AD).

AD, also known as atopic eczema, is one of the most common chronic skin diseases, affecting 1 - 3% of adults worldwide.[1] Data from the National Health Interview Survey, a United States (US) population-based household survey, indicate that the prevalence of childhood AD steadily increased from approximately 8% in 1997 to more than 12% in 2010 and 2011.[2] AD is often characterized by pruritus, erythema, edema, xerosis, erosions/excoriations, oozing, crusting, and lichenification. In addition, sleep disturbance commonly occurs with AD, due in large part to the significant itching associated with the disease.[3,4] AD is also associated with multiple other comorbid conditions, including a higher prevalence of other atopic diseases such as rhinitis, food allergies, and asthma, with the severity of AD directly related to the severity of the comorbidities.[5]

The pathophysiology of AD is influenced by a complex interplay between inflammation, environmental factors, genetics, and skin barrier dysfunction. AD is driven by multiple immune pathways that create different disease features.[6-11] Two T-cell subsets, Th2 and Th22, are commonly present and activated across major subtypes of AD. Specific subtypes of AD, including Asian-origin, pediatric, and intrinsic AD, have a prominent interleukin (IL)-17 component, as well as tissue patterning that overlaps with distinctive psoriasis histopathology.[12] There is also evidence that the Th17/IL-23 axis is up-regulated in patients with AD and that it might have a role in AD development.[13,14] Further, it has been shown that IL-23 is released in human skin after scratching, which polarizes human skin dendritic cells to drive an IL-22 response of epidermal thickening, supporting the utility of IL-23 and IL-22 blockade in AD.[15] Hence, AD might best be considered a multi-axis immune disease with involvement of the Th2, Th22, and potentially Th17 pathways.

The goal of AD treatment is to reduce skin inflammation, and the treatment options depend on the extent and severity of disease. Topical agents, such as corticosteroids, calcineurin inhibitors, and moisturizers, are commonly used alone for mild to moderate cases. When topical therapies are insufficient for treating the signs and symptoms of AD, systemic therapy or phototherapy are generally added.[16] Oral immunosuppressants[17] like methotrexate or cyclosporin and glucocorticoids can be effective, but are frequently associated with severe toxicity and side effects, thus limiting their use to short courses and/or intermittent therapy.

Several biological agents, such as anti-tumor necrosis factor (TNF)-α (e.g., infliximab, etanercept), anti-immunoglobin (Ig)E (omalizumab), anti-IL-5 (mepolizumab), and anti-CD11a (efalizumab), have not shown efficacy in AD clinical studies. In a small Phase 2 study, ustekinumab, an IL-12/IL-23 blocking agent, showed a numerical improvement in clinical AD endpoints when compared to the placebo arm. Nonetheless, the study failed to achieve its primary endpoint as the difference was not statistically significant. The study used the same dosing regimen approved by the US Food and Drug Administration (FDA) for psoriasis.[18] On the other hand, dupilumab, an antibody directed to block both IL-4 and IL-13

signal transduction and therefore inhibiting the Th2 inflammatory pathway, was approved by the US FDA in March 2017 and the European Commission in September 2017. In two Phase 3 studies, dupilumab significantly improved the signs and symptoms of AD compared with placebo,[19] with injection site reactions, conjunctivitis, blepharitis, and oral herpes reported as the most common adverse reactions in the studies.[20] Although dupilumab addresses the needs of some patients with moderate to severe AD, a large unmet need for short- and long-term efficacious treatments still exists in this population.

Despite the availability of various topical AD therapies, many patients still do not respond adequately to these treatments, and there are limited systemic treatment options available. Since the IL-23/Th17 axis is overexpressed in AD, this target may have therapeutic potential. Among AD patients, IL-23/Th17 expression has been shown to be higher in various AD subpopulations (i.e., Asian population, pediatric population, intrinsic/non-allergic subtype [normal levels of IgE]).[8]

Risankizumab is a fully humanized monoclonal antibody (mAb) of the IgG1 subclass directed towards IL-23 p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23. Risankizumab is currently being developed for the treatment of psoriasis (Phase 3 studies concluded) and Crohn's disease (currently in Phase 3 studies), as well as the treatment of ulcerative colitis, and psoriatic arthritis (in Phase 2 studies), and may address the current needs for subjects with AD.

The current study compares the safety and efficacy of risankizumab versus placebo for the treatment of moderate to severe AD in adult and adolescent subjects. For a more detailed description of the risankizumab drug profile, refer to the latest version of the Investigator's Brochure (IB).[21]

Clinical Hypothesis

Risankizumab will provide superior efficacy compared to placebo and will be well tolerated in subjects with moderate to severe AD.

2.2 Benefits and Risks to Subjects

This proof-of-concept (POC) study is required to learn more about the potential treatment effect of risankizumab in AD. While IL-23/Th17 has been identified as a potential target in AD, the pathway is predominantly overexpressed in subsets of AD patients and has not been definitively confirmed as a viable target in clinical studies. With minimal clinical data on IL-23 in AD, a robust POC study is needed to learn about the safety and efficacy of risankizumab in the general AD patient population and at different doses.

As with many immune modulating agents, risankizumab may impair immune function, resulting in a risk of infection. This will be monitored by collection of all adverse events (AEs) during the treatment and observation periods. In addition, subjects with active infection will not be included in the study.

Subjects with a positive QuantiFERON®-TB (or interferon gamma release assay [IGRA] equivalent)/tuberculosis (TB) skin test result for TB must fulfill entry criteria as specified in Section 5.1 of this protocol. IL-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[22,23] No cases of active TB have been reported across all risankizumab studies to date. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were

concurrently treated with risankizumab and appropriate TB prophylaxis during the study, none developed active TB during a mean follow-up period of 61 weeks. Of the 31 subjects from Study M15-992 (IMMhance) with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on risankizumab. Thus, low-risk subjects with positive QuantiFERON-TB testing (or IGRA equivalent)/TB skin test do not need to be treated with anti-TB therapy prior to receiving risankizumab, but should be carefully monitored for any sign of TB reactivation.

Published literature indicates that inhibition of IL-23 is unlikely to increase the risk for cancer. Expression of IL-23 is increased in human tumors.[24-26] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models. However, while there is not enough clinical information at this time to rule out a risk of cancer with risankizumab, this risk is considered small.

Although rare, a potential for hepatic AEs is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.

Increases in major adverse cardiovascular events (MACE), including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or nonserious) observed in this study will be adjudicated by an independent committee. An independent Cardiovascular Adjudication Committee (CAC) will adjudicate all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation (Section 6.3).

Local reactions to subcutaneously-administered biologic therapies are usually limited to redness, swelling, or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study drug administration. An independent Anaphylaxis Adjudication Committee (AAC) will adjudicate observed systemic hypersensitivity and anaphylactic events. The AAC will remain blinded to treatment allocation (Section 6.4).

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[27] Based on data from the integrated safety analyses, risankizumab is safe and well-tolerated and demonstrates a favorable benefit-risk profile.

For further details, please see findings from completed studies, including safety data, in the risankizumab IB.[21]

In view of the Coronavirus Disease – 2019 (COVID-19) pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated based on real world and clinical trial data. At this time, the effects of risankizumab on the course of COVID-19 are not well defined.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this study is to assess the safety and efficacy of risankizumab for the treatment of moderate to severe AD in adult and adolescent subjects.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving at least a 75% reduction from Baseline in Eczema Area and Severity Index (EASI 75) at Week 16.

3.3 Secondary Endpoints

Key Secondary Endpoints

The key secondary endpoints for this study are:

1. The proportion of subjects achieving validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD) of "0" or "1" (on a 5-point scale) with a reduction from Baseline of ≥ 2 points at Week 16.
2. The proportion of subjects achieving a reduction of ≥ 4 points in worst pruritus numerical rating scale (NRS) from Baseline to Week 16.

Other Secondary Endpoints

Other secondary endpoints for each of the specified time points include:

- Percent change in EASI from Baseline to Week 16, Week 28, and Week 52.
- Proportion of subjects achieving EASI 75 at Week 28 and Week 52.
- Proportion of subjects achieving EASI 50 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving EASI 90 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving vIGA-AD of "0" or "1" with a reduction from Baseline of ≥ 2 points to Week 28 and Week 52.
- Change in body surface area (BSA) from Baseline to Week 16, Week 28, and Week 52.
- Proportion of subjects achieving 50% improvement in SCORing Atopic Dermatitis (SCORAD 50) at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving SCORAD 75 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving SCORAD 90 at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving Dermatology Life Quality index (DLQI) of "0" or "1" at Week 16, Week 28, and Week 52.

- Proportion of subjects achieving Children's Dermatology Life Quality index (CDLQI) of "0" or "1" at Week 16, Week 28, and Week 52.
- Proportion of subjects achieving a DLQI improvement of ≥ 4 points at Week 16, Week 28, and Week 52 among subjects with a DLQI ≥ 4 at Baseline.
- Change in DLQI from Baseline to Week 16, Week 28, and Week 52.
- Change in CDLQI from Baseline to Week 16, Week 28, and Week 52.
- Change in worst pruritus NRS from Baseline to Week 16, Week 28, and Week 52.
- Proportion of subjects achieving a reduction of ≥ 4 points in worst pruritus NRS from Baseline to Week 28 and Week 52.

Additional Endpoints

All variables listed as primary or secondary endpoints will be analyzed at all visits in addition to those listed above. In addition, the following additional endpoints will be evaluated at applicable visits:

- Proportion of subjects achieving EASI 100.
- Proportion of subjects achieving vIGA-AD of "0" with a reduction from Baseline of ≥ 2 points.
- Percent change in SCORAD from Baseline.
- Change from Baseline in Patient Oriented Eczema Measure (POEM).
- Proportion of subjects achieving an improvement (reduction) in POEM of ≥ 4 from Baseline among subjects with a POEM ≥ 4 at Baseline.
- Change from Baseline in Patient Global Impression of Severity (PGIS).
- Proportion of subjects who report symptoms to be "Minimal" or "Absent" for PGIS.
- Proportion of subjects who have "Very much improved" or "Much improved" for Patient Global Impression of Change (PGIC).
- Change from Baseline in Atopic Dermatitis Symptom Scale (ADerm-SS) total score.
- Change from Baseline in ADerm-SS skin pain score.
- Change from Baseline in Atopic Dermatitis Impact Scale (ADerm-IS) total score.
- Change from Baseline in ADerm-IS sleep domain score.
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS total score ≥ minimal clinically important difference (MCID) from Baseline for subjects with ADerm-SS total score ≥ MCID at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-SS skin pain score ≥ MCID from Baseline for subjects with ADerm-SS skin pain score ≥ MCID at Baseline.
- Proportion of subjects achieving an improvement (reduction) in ADerm-IS total score ≥ MCID from Baseline for subjects with ADerm-IS total score ≥ MCID at Baseline.

- Proportion of subjects achieving an improvement (reduction) in ADerm-IS sleep disturbance score ≥ MCID from Baseline for subjects with ADerm-IS sleep disturbance score ≥ MCID at Baseline.
- Change from Baseline in EuroQoL-5D-5L (EQ-5D-5L).

3.4 Safety Endpoints

Safety evaluations include adverse event (AE) monitoring, vital sign measurements, electrocardiogram (ECG) variables, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic and Immunogenicity Endpoints

Serum risankizumab concentrations, anti-drug antibodies (ADA), and neutralizing antibodies (nAb) will be determined from blood collected by venipuncture at the visits indicated in the Activity Schedule (Appendix D).

3.6 Biomarker Research

Optional blood, skin biopsy, and skin tape samples for biomarker research will be collected as described in the Activity Schedule (Appendix D). Prognostic and predictive biomarker signatures may be evaluated. Biomarker assessments may include, but are not limited to, nucleic acids, proteins, metabolites, or lipids. The objective of biomarker research is to analyze samples that will help to understand AD, related conditions, and the subject's response to risankizumab. Genes of interest may include (but are not limited to) those associated with pharmacokinetics (PK), genes within the target pathway (IL-23, Janus kinase [JAK]/signal transduction activators of transcription [STAT], tyrosine kinase [TYK]2), or other genes believed to be related to AD and other inflammatory diseases (caspase recruitment domain [CARD]-containing),[11] filaggrin, human leukocyte antigen [HLA], IL). Blood and skin samples may be used to investigate genetic, epigenetic, transcriptomic, proteomic, metabolomic, metagenomic, phenotypic, functional, and targeted investigations related to AD, related conditions, and response to risankizumab.

AbbVie (or people or companies working with AbbVie) will store the biomarker exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on risankizumab (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, randomized, double-blind, placebo-controlled multicenter study to evaluate the safety and efficacy of risankizumab for the treatment of moderate to severe AD in adult and adolescent subjects with a confirmed diagnosis and onset of symptoms at least 2 years before the Baseline Visit.

The duration of the study will be up to 65 weeks and will include a screening period of up to 35 days, a 16-week double-blind treatment period (Period A), and a 36-week double-blind treatment period (Period B). In addition, subjects will have a telephone follow-up call 20 weeks after their last dose of risankizumab to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs.

This study plans to enroll approximately 155 subjects from up to 75 sites in the US, Canada, Japan, and Australia, although the number, allocation, and location of sites may vary depending on operational aspects of the study. Approximately 20% of subjects will come from sites in Japan. Subjects who meet eligibility criteria (see Section 5.1) will be randomized at Baseline in a 2:2:1 ratio to one of 3 treatment groups: (1) risankizumab 150 mg (62 subjects), (2) risankizumab 300 mg (62 subjects), or (3) matching placebo (31 subjects). In Period A, subjects will receive their randomized treatment as subcutaneous (SC) injections at Week 0 and Week 4.

Once a sufficient number of subjects to fulfill the enrollment target have entered the screening process, no further subjects will be screened. Once 155 subjects have been randomized, subjects who have started screening but have not yet been randomized will be allowed to enroll in the study if eligible.

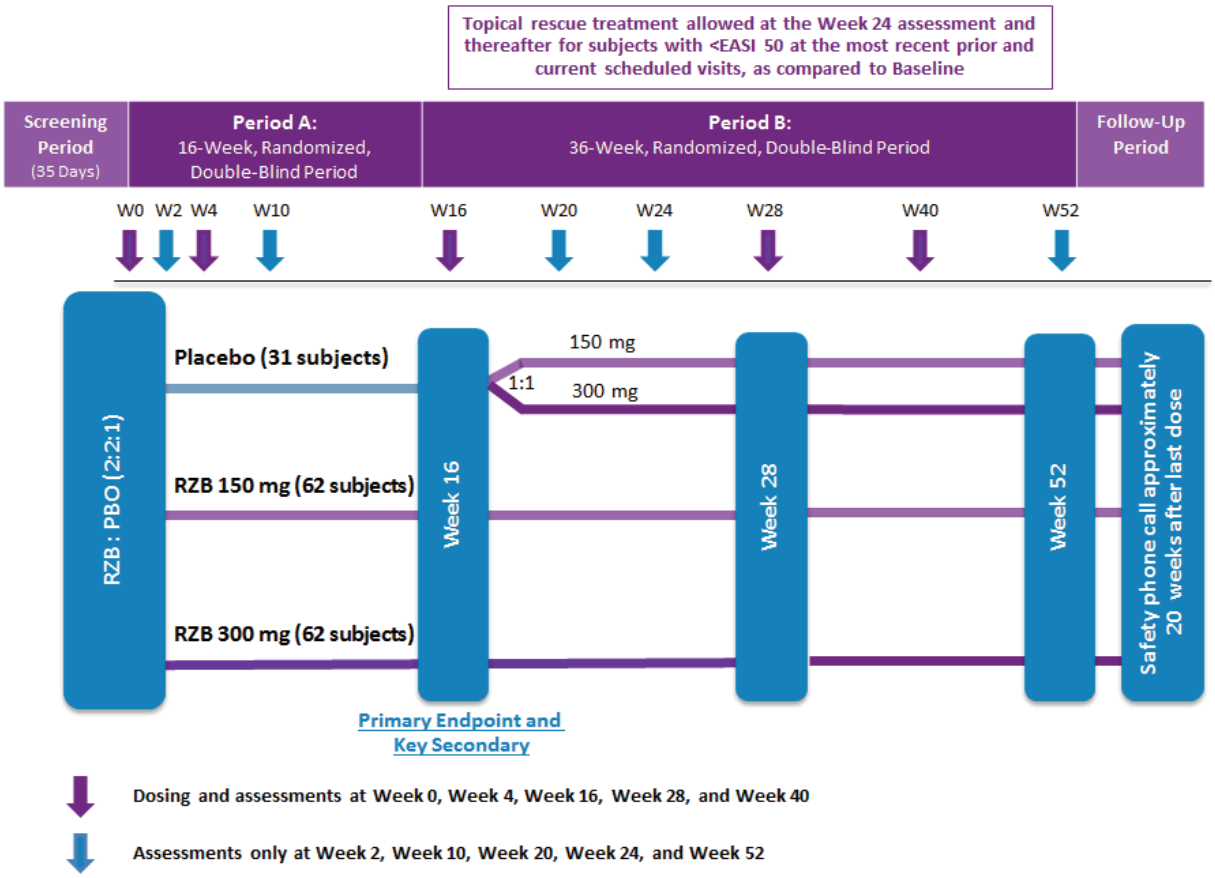
The primary analysis will be performed when all subjects complete Week 16. The Week 16 evaluation is the final analysis for the primary endpoint of EASI 75 and key secondary endpoints of vIGA-AD response and pruritus NRS reduction. At the Week 16 analysis, the sponsor will be unblinded, although study sites and subjects will remain blinded for the duration of the study.

In Period B, subjects in the placebo group will be re-randomized at Week 16 in a 1:1 ratio to receive either risankizumab 150 mg or 300 mg for the remainder of the study. Subjects originally randomized to the risankizumab 150 mg or 300 mg arms will stay on their previously-assigned treatment through the end of the study. Subjects will receive their randomized treatment as SC injections at Week 16, Week 28, and Week 40. During Period B, subjects with < EASI 50 response, as compared to Baseline, at the most recent prior and current scheduled visits will be allowed to begin approved concomitant rescue treatment after the assessments at the Week 24 visit and at any visit thereafter (see Section 5.4).

Subjects who prematurely discontinue study drug should complete a Premature Discontinuation (PD) Visit as soon as possible, preferably within 2 weeks of discontinuation. Subjects who prematurely discontinue study drug should continue to be followed for safety and efficacy assessments at all regularly scheduled visits unless they have decided to discontinue study participation entirely (withdrawal of informed consent). See Section 5.6 for information regarding early discontinuation.

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

Figure 1. Study Schematic



EASI = Eczema Area and Severity Index; PBO = placebo; RZB = risankizumab; W = week

4.2 Discussion of Study Design

Choice of Control Group

A placebo control has been selected as the appropriate control group for this study to establish an unbiased efficacy and safety profile of risankizumab in subjects with AD.

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

Adult and adolescent subjects who have moderate to severe AD (defined as an EASI ≥ 16, BSA ≥ 10%, and vIGA-AD score ≥ 3 at the Baseline Visit), with onset of symptoms at least 2 years prior to Baseline,

are eligible for this study. The criteria relating to safety have been selected to allow subjects to be safely enrolled and treated with risankizumab based on the current knowledge of this drug.

Selection of Doses in the Study

Two dose levels of risankizumab have been selected for evaluation in this study. The risankizumab 150 mg SC dose has demonstrated efficacy in Phase 3 clinical trials for psoriasis and could be efficacious in subjects with AD. The additional higher dose of risankizumab 300 mg SC was selected since AD is a disease with a high inflammatory burden. The risankizumab 300 mg dose, along with the 150 mg dose, is expected to provide dose/exposure-response data to allow for evaluation of the efficacy plateau. Both doses are within the range of doses safely administered in previous risankizumab clinical studies.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent** prior to the initiation of any screening or study-related procedures. Where locally permitted and approved, subjects ≥ 12 and < 18 years of age (hereafter referred to as "adolescent subjects") must sign an assent approved by an independent ethics committee (IEC)/institutional review board (IRB). For adolescent subjects, the investigator or his/her representative will explain the nature of the study to both the subject and the subject's parent/legal guardian, and answer all their questions regarding this study. Additionally, the informed consent statement will be reviewed and signed and dated by the subject's parent/legal guardian, the person who administered the informed consent, and any other signatories according to local requirements prior to any study-related screening procedures being performed on the subject. If a subject becomes of legal age during the course of the study, that subject will need to voluntarily sign and date the current version of the informed consent at their next study visit.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old and functionally able to read and understand study questionnaires. Where locally permissible and approved, male or female adolescent subjects (at least 12 years old) may participate.
- 3. **Body weight ≥ 40 kg** at the Baseline Visit for subjects between ≥ 12 and < 18 years of age.
- 4. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) < 2 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) < 2 × ULN;

- Serum total bilirubin ≤ 2.0 mg/dL, except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
- Total white blood cell (WBC) count > 3,000/µL;
- Absolute neutrophil count (ANC) > 1,500/µL;
- Platelet count > 100,000/µL;
- Hemoglobin > 8.0 g/dL.

✓ 5. Willing and/or able to comply with procedures required in this protocol.

AD Disease Activity

✓ 6. Diagnosis of AD with onset of symptoms at least 2 years prior to Baseline and subject meets Hanifin and Rajka criteria.[28]

✓ 7. Inadequate response to treatment with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI), or subject for whom topical treatments are otherwise medically inadvisable (e.g., because of side effects or safety risks). Subjects are potentially eligible after appropriate washout (10 days prior to Baseline visit).

✓ 8. Moderate to severe AD, defined by EASI ≥ 16, BSA ≥ 10%, and a vIGA-AD score ≥ 3 at the Baseline Visit.

✓ 9. Twice-daily use of an additive-free, bland emollient for at least 7 days prior to Baseline and throughout duration of the study is required.

✓ 10. Baseline weekly average of daily worst pruritus NRS ≥ 4. (Note: The baseline weekly average of daily worst pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline Visit. A minimum of 4 daily scores out of the 7 days is needed.)

Subject History

✓ 11. No evidence of **hepatitis B (HBV) or hepatitis C (HCV) infection**, defined as:

- HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody [HBs Ab] positive [+] subjects where mandated by local requirements).
- HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab).

✓ 12. No evidence of **human immunodeficiency virus (HIV)**, defined as confirmed positive anti-HIV antibody (HIV Ab) test.

✓ 13. No case of **active TB**. Subjects with a positive QuantiFERON-TB gold test (or IGRA equivalent) or TB skin test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB. If presence of latent TB is established, subjects are not required to be treated with prophylactic anti-TB therapy prior to or during the study, if the subject is considered low risk for reactivation per investigator judgment.

- 14. No **active systemic infection** during the last 2 weeks prior to Baseline Visit (exception: common cold), as assessed by the investigator.
- 15. No documented **active or suspected malignancy** or history of **any malignancy** within the last 5 years except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
- 16. No history of organ transplantation.
- 17. No **major surgery** performed within 12 weeks prior to randomization or planned during the conduct of the study (e.g., hip replacement, aneurysm removal, stomach ligation).
- 18. No historical or concurrent clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition, that the investigator determines would compromise the safety or **interfere with the subject's participation** in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the protocol; as well as being permanently wheelchair-bound or bedridden or having very poor functional status, preventing the ability to perform self-care.
- 19. No **presence of skin comorbidities** that could interfere with study assessment of AD.
- 20. No **skin infections** (bacterial, fungal, or viral) requiring intravenous (IV) systemic treatment within 4 weeks of the Baseline Visit.
- 21. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months, including medicinal or recreational cannabis or cannabinoids.
- 22. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 23. Subject is judged to be in good general health, as determined by the principal investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead ECG performed during the Screening period.

Contraception

- 24. For all females of child-bearing potential, a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at Baseline prior to the first dose of study drug.
- 25. **If female**, subject must be of non-childbearing potential OR a female of childbearing potential practicing at least 1 protocol-specified **method of birth control**, that is effective from Study Day 0 through at least 140 days (20 weeks or as guided by the local risankizumab label (if approved), whichever is longer) after the last dose of study drug (local practices may require 2 methods of birth control).
- 26. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for at least 140 days (20 weeks or as guided by the local risankizumab label (if approved), whichever is longer) after the last dose of study drug.

Prior/Concomitant Medications

- 27. No prior exposure to any **biologic immunomodulatory agent**, including but not limited to anti-IL-23 (e.g., risankizumab, guselkumab), anti-IL-4R (e.g., dupilumab), anti-IL12/23 (e.g., ustekinumab), anti-IL-17 (e.g., secukinumab), or anti-IgE (e.g., omalizumab).
- 28. No prior exposure to any systemic or topical JAK inhibitor (including but not limited to tofacitinib, baricitinib, upadacitinib, ruxolitinib, and filgotinib).
- 29. No exposure to systemic therapy that can also be used for the treatment of AD, including but not limited to corticosteroids, methotrexate (MTX), cyclosporine, azathioprine (AZA), phosphodiesterase type 4 (PDE4)-inhibitors, and mycophenolate mofetil, within 4 weeks prior to the Baseline Visit.
- 30. No use of TCS, TCI, prescription moisturizers, or moisturizers containing additives such as, but not limited to, ceramide, hyaluronic acid, urea, heparin, or filaggrin within 10 days prior to the Baseline Visit.
- 31. No use of traditional Chinese medicines within 4 weeks prior to the Baseline Visit and during the study.
- 32. No phototherapy treatment, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks prior to the Baseline Visit and throughout the duration of the study.
- 33. Subject must not have received **any live vaccine** within 6 weeks prior to the first dose of study drug (Baseline), or expects need of live vaccination during study participation, including at least 140 days (20 weeks or as guided by the local risankizumab label (if approved), whichever is longer) after the last dose of study drug.
- 34. Subject must not have been treated with **any other investigational drug** within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or be currently enrolled in another clinical study.

5.2 Contraception Recommendations

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 international unit (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(s) and for at least 20 weeks (140 days or as guided by the local risankizumab label (if approved), whichever is longer) after the last dose of study drug. Females must commit to one of the following methods of birth control:

  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline (Study Day 0).
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline (Study Day 0).
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - Vasectomized sexual partner(s) (the vasectomized partner[s] has received medical assessment of the surgical success and is the sole sexual partner of the study subject).
  - True abstinence: 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 guidelines, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

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

5.3 Prohibited Medications and Therapy

Use of the following treatments is prohibited throughout the study:

1. Any immunomodulatory systemic biologic. Examples of biologic therapies include but are not limited to the following:
   - Zolair® (omalizumab);
   - Dupixent® (dupilumab);
   - Rituximab or biosimilar version.
2. Systemic non-biologic therapy for AD, including but not limited to JAK inhibitors (including but not limited to ruxolitinib, tofacitinib, baricitinib, upadacitinib, and filgotinib), MTX, cyclosporine, AZA, PDE4-inhibitors, and mycophenolate mofetil.

3. Oral, parenteral, intramuscular, and intralesional corticosteroids. However, use of inhaled, topical ophthalmic, or intranasal corticosteroids is permitted during the study.
4. Phototherapy treatment (ultraviolet B [UVB] or ultraviolet A [UVA] phototherapy, including psoralen and UVA [PUVA]), laser therapy, tanning booth, or extended sun exposure.
5. Topical treatments for AD, including but not limited to topical JAK inhibitors, calcineurin inhibitors, corticosteroids, prescription moisturizers, or moisturizers containing additives such as, but not limited to, ceramide, hyaluronic acid, urea, heparin, or filaggrin. Exceptions: rescue treatment (i.e., TCS) started after Week 24 assessment (Section 5.4) and the required additive-free, bland emollient treatment (Section 5.4).
6. Wet wrap therapy, regardless of the topical agent used.
7. Live attenuated vaccines are not permitted during study participation and including up to 140 days (20 weeks or as guided by the local risankizumab label (if approved), whichever is longer) after the last dose of study drug. Examples of live attenuated vaccines include, but are not limited to, the following:
    - Bacille Calmette-Guérin (BCG)
    - Zoster vaccine live (Zostavax)
    - Measles-mumps-rubella or measles mumps rubella varicella
    - Monovalent live attenuated influenza A (intranasal)
    - Oral polio vaccine
    - Rotavirus
    - Seasonal trivalent live attenuated influenza (intranasal)
    - Smallpox
    - Oral typhoid vaccine
    - Varicella (chicken pox)
    - Yellow fever
8. Medicinal or recreational cannabis or cannabinoid use.
9. Traditional Chinese medicines.
10. Investigational drugs are prohibited during the study.

5.4 Prior and Concomitant Therapy

Required Concomitant Therapy

All subjects are required to use an additive-free, bland emollient twice daily for at least 7 days prior to Baseline (Study Day 0) and throughout the course of the study. To allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Allowed Concomitant Therapy

Stable doses of other concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the subject from participation, are permissible. All concomitant medications should be carefully evaluated by the investigator, and the clinical monitor should be contacted when there are questions regarding concomitant medications.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has received from 4 weeks prior to screening 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).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with risankizumab can be located in the risankizumab IB.

Subjects must be able to safely discontinue any prohibited medications as specified in the eligibility criteria; where not specified, discontinuation must occur 5 half-lives or 4 weeks, whichever is longer, prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Rescue Therapy

Topical rescue treatment is allowed only after the assessments at the Week 24 visit and at any visit thereafter in subjects with < EASI 50 response, as compared to Baseline, at the most recent prior and current scheduled visits (e.g., < EASI 50 at Week 20 and Week 24 OR at Week 24 and Week 28, etc.). Rescue treatment is limited to up to twice-daily application of topical corticosteroids (TCS). (Note: Topical calcineurin inhibitors (TCIs) may be applied as rescue treatment to sensitive areas [e.g., facial, genital, and intertriginous areas]). Use of TCS and/or TCI as rescue treatment should be recorded on the appropriate concomitant medication eCRF.

Subjects who receive prohibited topical treatment prior to Week 24 assessment will be considered treatment failures; however, they will remain on the study treatment assigned at randomization.

Subjects who receive other systemic therapy for AD will be discontinued from study drug.

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent).

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject will be discontinued from study drug at any time for reasons including but not limited to the following:

- Clinically significant abnormal laboratory result(s) or AEs that preclude continuation of the study medication, as determined by the investigator and the AbbVie Therapeutic Area Medical Director (TA MD) (as applicable).

- The investigator believes withdrawal from the study is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation(s) are noted after the subject started study drug, if continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD, after consultation with the investigator.
- Subject needs to initiate prohibited medication(s) or dosages, and continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Subject is noncompliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Subject becomes pregnant while participating in the study.
- Subject is diagnosed with a malignancy. (Exception: localized NMSC or carcinoma in-situ of the cervix, where discontinuation is at the discretion of the investigator.)
- Subject is significantly noncompliant with study procedures.
- Occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample):
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5;
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

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

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.

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 all acceptable mitigation steps have been explored.

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

5.6 Follow-Up for Subject Withdrawal from Study

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

Subjects who prematurely discontinue study drug should complete a PD Visit as soon as possible, preferably within 2 weeks of discontinuation. Samples for PK and immunogenicity will be collected during the PD Visit. Afterwards, subjects should follow the regular visit schedule as outlined in the Activity Schedule (Appendix D) and adhere to all study procedures except for dispensing study drug, PK sample collection and blood sample collection for optional exploratory research. Once the subject has discontinued study drug, all rescue- and efficacy-driven discontinuation criteria no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

In addition, if subject is willing and has not withdrawn consent, a follow-up phone call 20 weeks after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

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

5.7 Study Drug

Information about the study drug and placebo used in this study is presented in (Table 1).

Table 1. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe (PFS)	75 mg/0.83 mL (90 mg/mL)	SC injection	Boehringer-Ingelheim Pharma GmbH & Co. KG
Placebo for risankizumab (ABBV-066)	Solution for injection in PFS	N/A	SC injection	Boehringer-Ingelheim Pharma GmbH & Co. KG

PFS = pre-filled syringe; SC = subcutaneous

During Period A, study site staff will administer study drug subcutaneously as follows:

- Risankizumab 150 mg (2 × 75 mg PFS and 2 × placebo PFS)
- Risankizumab 300 mg (4 × 75 mg PFS), or
- Matching placebo (4 × placebo PFS).

During Period B, study site staff will administer either risankizumab 150 mg or risankizumab 300 mg subcutaneously as described above.

AbbVie will not supply drug other than risankizumab and matching placebo. If a subject is unable to come to the study site for a study visit due to the COVID-19 pandemic, study drug can be taken to the subject's house and administered by trained site personnel under appropriate conditions.

Risankizumab and matching placebo will be packaged in quantities sufficient to accommodate study design. Each kit will be labeled per local requirements, and this label must remain affixed to the kit. Upon receipt, study drug must be kept in the original packaging in a secured limited access storage area. Study drug must be kept refrigerated between 2°to 8°C (36°to 46°F), and a temperature log must be maintained for documentation.

Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Interruption/Discontinuation of Study Drug Due to COVID-19

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

5.8 Randomization/Drug Assignment

Each subject will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the identification number assigned by the IRT at the initial screening visit should be used. In addition, the IRT will assign a unique randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. At Baseline (Study Day 0), subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to risankizumab 150 mg (N = 62), risankizumab 300 mg (N = 62), or matching placebo (N = 31). Randomization will be stratified by baseline disease severity (moderate [vIGA-AD 3] versus severe [vIGA-AD 4]) and geographic region (Japan versus rest of world).

At Week 16, subjects in the placebo group will be re-randomized in a 1:1 ratio to receive either risankizumab 150 mg or 300 mg for the remainder of the study. Subjects originally randomized to the risankizumab 150 mg or 300 mg arms will stay on their previously-assigned treatment through the end of the study.

While the sponsor will be unblinded as part of the Week 16 analysis, the investigator, study site personnel, and the subject will remain blinded to each subject's treatment for the duration of the study.

To maintain the blind, the risankizumab PFS and placebo PFS provided for the study will be identical in appearance and number of syringes.

In the event of a medical emergency in which the investigator believes that knowledge of study drug treatment is required, reasonable efforts must be made to contact the AbbVie Emergency Contact prior to breaking the blind, as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary that warrants breaking the blind prior to contacting the AbbVie Emergency Contact, the investigator can directly access the IRT system to break the blind without AbbVie agreement.

The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

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 for notifying the IEC/IRB, regulatory authorities (as applicable), and AbbVie.

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/AEs and SAEs

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.

An AE 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 an AE only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria, and/or the investigator considers it to be an AE.

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

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 140 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

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

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

In the event that an enrolled subject experiences an AE related to asthma, additional information will be collected utilizing a supplemental asthma CRF.

Areas of Safety Interest

Infections, especially opportunistic infections, are a potential risk with immunomodulators. Subjects will be screened and monitored throughout the study for infections and other areas of safety interest (ASI) (Table 2). Screening procedures are outlined in the Activity Schedule (Appendix D).

If any of the following AEs are reported, then the following supplemental report must be completed.

Table 2. Areas of Safety Interest

Adverse Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Cerebral vascular accident** **Cardiovascular death**	• Cardiovascular History and CV Risk Factors eCRF • Cardiovascular (Cardiac) AE eCRF • Myocardial Infarction and Unstable Angina AE eCRF • Heart Failure AE eCRF • Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF • Combination Thrombotic Event AE eCRF • Arrhythmia AE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **Hepatic-related SAE**	Hepatic AE eCRF
Hypersensitivity reactions	Hypersensitivity Reaction Signs and Symptoms eCRF
TB Subjects will be screened for TB (using the TB Screening Form) and those with active TB will be excluded from participation in the study. Subjects with events of latent TB or suspected active TB after initiation of study drug should have a TB Supplemental Form completed.	• TB Screening eCRF • TB Supplemental eCRF
Death	Death eCRF

AE = adverse event; CV = cardiovascular; eCRF = electronic case report form; SAE = serious adverse event; TB = tuberculosis

AE Severity and Relationship to Study Drug

AEs must be graded to the 5 criteria as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V5.0,[29] which can be accessed at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

If no specific criteria per CTCAE V5.0 guidelines are available for the reported event, the event should be graded per the Investigator's judgment:

- Grade 1 (Mild); asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate); minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3 (Severe); medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4 (Severe); Life-threatening consequences; urgent intervention indicated.

- Grade 5 (Severe); Death related to AE.

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

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5).

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

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.

6.2 Independent Data Monitoring Committee

An external independent data monitoring committee (IDMC) will review unblinded safety data on a cohort level throughout the course of the study.

- A separate IDMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the IDMC members, frequency and triggers of data reviews, and relevant safety data to be assessed. Unblinded adjudicated cardio-cerebrovascular events per the CAC charter and anaphylaxis events per the AAC charter will be presented to the IDMC for review on a periodic basis.
- Communications from the IDMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

6.3 Cardiovascular Adjudication Committee

An independent adjudication committee will be adjudicating all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the CAC Adjudication Committee Charter. Dedicated eCRFs will be used as outlined in Table 2.

In addition, the site may be contacted for additional source documentation for relevant events.

6.4 Anaphylaxis Adjudication Committee

While no concerns with systemic hypersensitivity have been identified with the use of risankizumab, the sponsor has established an independent, blinded expert committee to adjudicate events of anaphylaxis based on a pre-specified definition. This independent external AAC will adjudicate observed suspected anaphylactic reactions and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the AAC Charter. A supplemental Hypersensitivity Reactions eCRF will be used to collect information pertinent to the events. In addition, the site may be contacted for additional source documentation for relevant events.

If a systemic hypersensitivity reaction such as anaphylaxis is suspected while the subject is not on site, every effort should be made to obtain tryptase and histamine levels from the treating facility to help better understand and characterize the diagnosis. If a suspected systemic hypersensitivity reaction occurs on site, in addition to testing tryptase and histamine levels, PK and ADA/nAb samples will also be collected.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The objective of the statistical analysis is to evaluate the safety and efficacy of risankizumab in comparison with the placebo group for the treatment of moderate to severe AD in adult and adolescent subjects. The primary analysis will be performed when all subjects complete Week 16. This analysis is the final and only analysis for the primary and key secondary endpoints.

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

7.2 Definition for Analysis Populations

The Intention-to-Treat (ITT) Population includes all randomized subjects and will be used for efficacy analyses. Subjects will be analyzed according to treatment as randomized.

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

The Safety Population consists of all randomized subjects who receive at least 1 dose of study drug. The safety analyses for each treatment period include subjects who receive at least 1 dose of study drug during that treatment period. Subjects will be analyzed based on the treatment they actually receive, regardless of the treatment to which they are randomized.

An "All Risankizumab" Treated Population (ALL_RISA) will consist of all subjects who received at least 1 dose of risankizumab in the study. This population will be used to provide a comprehensive summary of safety.

7.3 Statistical Analyses for Efficacy

Pairwise comparison of the primary endpoint and the key secondary endpoints will be conducted between each risankizumab group (risankizumab 150 mg and 300 mg, respectively) versus the placebo group using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline disease severity (moderate [vIGA-AD 3] versus severe [vIGA-AD 4]). For the analysis of the primary endpoint and key secondary endpoints, non-responder imputation (NRI) with multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C) will be used as the primary approach. The non-responder imputation with no special data handling for missing data due to COVID-19 (NRI-NC) approach, observed cases (OC) approach, and MI may be conducted as appropriate sensitivity analyses to handle missing values.

Efficacy data for subjects who switch to rescue medications will be imputed from the point of rescue using an NRI approach for the primary endpoint and key secondary endpoints.

Sample Size Estimation

Approximately 155 subjects will be randomized to risankizumab 150 mg, risankizumab 300 mg, or placebo in a ratio of 2:2:1 at Baseline (62 subjects each for the risankizumab 150 mg and 300 mg groups and 31 subjects for the placebo group). Assuming a maximum EASI 75 response rate of 15% in the placebo group, this sample size will provide at least 90% power to detect the treatment difference of at least 36% between each risankizumab group and placebo group using a two-sided test at a 0.025 significance level. The graphic approach for controlling multiplicity will be outlined in the SAP.

7.4 Statistical Analyses for Safety

All safety analyses will be performed on the Safety Population for both treatment periods, respectively, based on the treatment subjects actually receive. Safety will be assessed by AEs, laboratory tests, vital signs, and ECG variables. Missing safety data will not be imputed for safety analysis. Analysis details will be specified in the SAP. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE with onset or worsening on or after the first dose of study drug and within 140 days (20 weeks) after the last dose of study treatment injection. The number and percentage of subjects experiencing TEAEs will be tabulated using MedDRA system organ class (SOC) and preferred term (PT), as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (i.e., number, percentages, and events per 100 patient-years) of TEAEs, SAEs, deaths, AEs leading to discontinuation, and ASI will be provided. Pre-treatment AEs will be summarized separately.

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

7.5 Analyses of Pharmacokinetics and Immunogenicity

Serum risankizumab concentrations will be summarized at each sampling time point for each dose group using descriptive statistics. Population PK analyses combining data from this study and other studies of risankizumab may be performed and reported separately. The relationship between risankizumab concentrations and certain efficacy and/or safety variables of interest may be explored.

ADA titers will be tabulated for each subject at the respective study visits. The number and percentage of subjects with ADA and nAb will be calculated by dose group. As appropriate, the effect of ADAs on risankizumab PK, efficacy, and/or safety variable(s), and/or any additional analyses may be explored.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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

8.2 Ethical Conduct of the Study

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

In the event of a state of emergency due to the COVID-19 pandemic 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 of assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), study visit schedule modification, and home IP administration by trained site personnel to ensure continuity of treatment, where allowed. Refer to the Operations Manual in Appendix F for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

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 investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug, and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

The end of study is defined as the date of the last subject's last contact, which will be a follow-up phone call 20 weeks after the last dose.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	Anaphylaxis Adjudication Committee
ACQ-5	Asthma Control Questionnaire-5
AD	Atopic dermatitis
ADA	Anti-drug antibodies
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASI	Area of safety interest
AST	Aspartate aminotransferase
AZA	Azathioprine
BCG	Bacille Calmette-Guérin
BSA	Body surface area
CAC	Cardiovascular Adjudication Committee
CARD	Caspase recruitment domain
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenzsel
COVID-19	Coronavirus Disease - 2019
CRO	Contract research organization
CV	Cardiovascular
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5D-5L
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice

HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HDL-C	High-density lipoprotein cholesterol
HLA	Human leukocyte antigen
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
IB	Investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intention-to-treat
IU	International unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
JAK	Janus kinase
LDL-C	Low-density lipoprotein cholesterol
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular event
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation

MTX	Methotrexate
nAb	Neutralizing antibody
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
NRI-C	Non-responder imputation with multiple imputation to handle missing data due to COVID-19
NRI-NC	Non-responder imputation with no special data handling for missing data due to COVID-19
NRS	Numerical rating scale
OC	Observed cases
PCR	Polymerase chain reaction
PCS	Potentially clinically significant
PD	Premature discontinuation
PDE4	Phosphodiesterase Type 4
PFS	Pre-filled syringe
PG	Pharmacogenetic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
POC	Proof-of-concept
POEM	Patient-Oriented Eczema Measure
PPD	Purified protein derivative
PT	Preferred Term
PUVA	Psoralen and ultraviolet A
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAP-S	Statistical analysis plan supplement
SAS	Statistical Analysis System
SC	Subcutaneous
SCORAD	SCORing Atopic Dermatitis
SOC	System Organ Class
STAT	signal transduction activators of transcription
SUSAR	Suspected unexpected serious adverse reactions

TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TYK	Tyrosine kinase
ULN	Upper limit of normal
US	United States
UVA	Ultraviolet A
UVB	Ultraviolet B
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis
WBC	White blood count

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-813: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Risankizumab in Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 13 October 2020

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Strategy Team, Immunology
		Therapeutic Area MD, Immunology
		Data and Statistical Sciences
		Clinical Pharmacology and Pharmacometrics
		Clinical Program Development, Immunology
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the Screening and subsequent study visits. The individual activities and allowed modifications due to COVID 19 are described in detail in the Operations Manual (Appendix F).

Study Activities Table

Activity	Screening	*Baseline/Week 0*	Week 2	*Week 4*	Week 10	*Week 16*	Week 20	Week 24	*Week 28*	*Week 40*	Week 52/PD	Follow Up Call
	Day –35 to Day –1	Day 0	Day 14 (± 3 Days)	Day 28 (± 3 Days)	Day 70 (± 3 Days)	Day 112 (± 3 Days)	Day 140 (± 7 Days)	Day 168 (± 7 Days)	Day 196 (± 7 Days)	Day 280 (± 7 Days)	Day 365 (± 7 Days)	20 Weeks After Last Dose
Subject information and informed consent (and assent, where applicable)	✓											
Eligibility criteria	✓	✓										
Medical history	✓	✓										
Atopic dermatitis history	✓	✓										
Asthma symptoms (if applicable, using Asthma Control Questionnaire-5 [ACQ-5])		✓										
Demographics	✓											
Drug, tobacco (including e-cigarettes), and alcohol history	✓											
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB screening	✓										✓	
Investigator assessments (EASI, BSA, vIGA-AD)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Investigator assessment (SCORAD)		✓		✓		✓			✓		✓	
Patient reported outcomes (Worst Pruritus NRS, ADerm-SS, and ADerm-IS)	✓	✓	✓	✓	✓	✓			✓	✓	✓	
Patient reported outcomes (DLQI/CDLQI, POEM)		✓		✓		✓			✓	✓	✓	

Activity	Screening	Baseline/Week 0	Week 2	Week 4	Week 10	Week 16	Week 20	Week 24	Week 28	Week 40	Week 52/PD	Follow Up Call
	Day –35 to Day –1	Day 0	Day 14 (± 3 Days)	Day 28 (± 3 Days)	Day 70 (± 3 Days)	Day 112 (± 3 Days)	Day 140 (± 7 Days)	Day 168 (± 7 Days)	Day 196 (± 7 Days)	Day 280 (± 7 Days)	Day 365 (± 7 Days)	20 Weeks After Last Dose
Patient reported outcome (PGIS)		✓	✓	✓	✓	✓			✓	✓	✓	
Patient reported outcome (PGIC)			✓	✓	✓	✓			✓	✓	✓	
EQ-5D-5L, SCORAD (subject-reported items)		✓		✓		✓			✓		✓	
12-lead ECG	✓										✓	
Height (Screening only), weight, and waist circumference (adults)	✓										✓	
Height, weight, and waist circumference (of adolescent age at Baseline)	✓				✓				✓		✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Physical examination	✓	✓									✓	
FSH, serum pregnancy test at central laboratory	✓											
Urine pregnancy test (local)		✓		✓		✓			✓	✓	✓	
Central laboratory tests – Hematology and clinical chemistry	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	
Central laboratory tests – Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides		✓										
Central laboratory tests – TB screen (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local purified protein derivative [PPD] skin test)	✓										✓	

Activity	Screening Day –35 to Day –1	Baseline/Week 0 Day 0	Week 2 Day 14 (± 3 Days)	Week 4 Day 28 (± 3 Days)	Week 10 Day 70 (± 3 Days)	Week 16 Day 112 (± 3 Days)	Week 20 Day 140 (± 7 Days)	Week 24 Day 168 (± 7 Days)	Week 28 Day 196 (± 7 Days)	Week 40 Day 280 (± 7 Days)	Week 52/PD Day 365 (± 7 Days)	Follow Up Call 20 Weeks After Last Dose
Central laboratory tests – HIV screening, Hepatitis B and C screening, urinalysis	✓											
Central laboratory test - IgE levels		✓				✓					✓	
Blood samples for risankizumab ADA assay and nAb assay		✓		✓		✓					✓	
Blood samples for risankizumab PK assay				✓	✓	✓					✓	
In-clinic post-dose monitoring for hypersensitivity reactions		✓		✓		✓			✓	✓		
Randomization/drug assignment (for placebo subjects only at Week 16)		✓				✓						
Dispense handheld ePRO device	✓											
Collect handheld ePRO device						✓						
Optional Biomarker Samples (to be Collected Only if Subject Provides Consent)												
Whole blood pharmacogenetic (PG-DNA) (if not collected at Baseline, may be collected at Week 2, Week 4, Week 16, or at the Week 52/PD Visit)		✓										
Whole blood transcriptomic (PG-RNA)		✓	✓	✓		✓					✓	
Whole blood plasma		✓	✓	✓		✓					✓	
Whole blood serum		✓	✓	✓		✓					✓	
Biopsy – Lesional skin punch		✓		✓		✓					✓	
Biopsy – Non-lesional skin punch		✓				✓						

Activity	Screening	*Baseline/Week 0*	Week 2	*Week 4*	Week 10	*Week 16*	Week 20	Week 24	*Week 28*	*Week 40*	Week 52/PD	Follow Up Call
	Day –35 to Day –1	Day 0	Day 14 (± 3 Days)	Day 28 (± 3 Days)	Day 70 (± 3 Days)	Day 112 (± 3 Days)	Day 140 (± 7 Days)	Day 168 (± 7 Days)	Day 196 (± 7 Days)	Day 280 (± 7 Days)	Day 365 (± 7 Days)	20 Weeks After Last Dose
Skin tape harvest – Lesional		✓		✓		✓					✓	
Skin tape harvest – Non-lesional		✓				✓						

Note: Column headers in underlined italic font style denote dosing visit.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	01 May 2018
Version 2.0	04 June 2018
Version 3.0	13 February 2019
Administrative Change 1	23 May 2019
Version 4.0	29 July 2019

The purpose of this version is to incorporate necessary protocol modifications due to the COVID-19 pandemic 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 anticipated additional risk to subjects.
- Section 5.5 – added instructions to refer to Operations Manual for necessary changes to activities or procedures.
- Section 5.7 – provided instructions in the event of temporary study drug interruption/halt due to COVID-19 and that in the event the subject cannot complete an onsite visit, administration of study drug at the subject's house is to be performed by study staff if feasible and permitted by local regulations.
- Section 5.9 – clarified that protocol deviations may include modifications due to COVID-19.
- Section 7.3 – added NRI-C to incorporate handling of missing data due to COVID-19 as the primary approach and NRI-NC as sensitivity analysis.
- 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.
- 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.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M16-813

Indication: Risankizumab Versus Placebo for Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab, ABBV-066

FULL TITLE: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Risankizumab in Adult and Adolescent Subjects with Moderate to Severe Atopic Dermatitis

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] AbbVie Inc. Immunology Clinical Development 1 North Waukegan Road [redacted] North Chicago, IL 60064 USA **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Phone: Mobile: Email: [redacted]
Safety Concerns	Immunology Safety Team AbbVie Inc. Dept. R48S, Bldg. AP31-2 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 (847) 938-8737 Email: GPRD_SafetyManagement_Immunology@abbvie.com
SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations	[redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: Email: [redacted]
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214	Phone: +001 866-762-6209 (Toll free) +001 317-271-1200 (Local calls) Fax: +001 317-616-2362 For country-specific toll free numbers, please refer to Covance Lab Manual.
Pharmacokinetic Lab	AbbVie Deutschland GmbH & Co. KG Bioanalysis Large Molecules Knollstrasse 67061 Ludwigshafen Germany	Phone: +49 621-589-4847 Fax: +49 621-589-3184

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2 PROTOCOL ACTIVITIES BY VISIT

2.1 Individual Treatment Period Visit Activities

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

Activities are grouped by category (e.g., interview, exam, etc.). Collection of investigator assessment data is not permitted by remote or virtual visits. Further information about each activity is provided in Section 3.

SCREENING:

INTERVIEW	• Subject information and informed consent (and assent, where applicable) • Eligibility criteria • Medical history • Atopic dermatitis (AD) history	• Demographics • Drug, tobacco (including e-cigarettes), and alcohol history • Prior/concomitant therapy • Tuberculosis (TB) screening
PRO	• Dispense handheld electronic patient-reported outcome (PRO) device for initiation of daily data collection (if applicable) • Worst Pruritus Numerical Rating Scale (NRS)	• Atopic Dermatitis Symptom Scale (ADerm-SS) • Atopic Dermatitis Impact Scale (ADerm-IS)
EXAM	• Eczema Area and Severity Index (EASI) • Body surface area (BSA) • Validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD) • Adverse event (AE) assessment	• 12-lead electrocardiogram (ECG) • Height, weight, and waist circumference • Vital signs • Physical examination
CENTRAL LAB	• Follicle-stimulating hormone (FSH) (if applicable) • Serum pregnancy test (for all female subjects of childbearing potential) • Hematology	• Clinical chemistry • TB test • Human immunodeficiency virus (HIV), Hepatitis B and C screening • Urinalysis

BASELINE/WEEK 0 (STUDY DAY 0) VISIT:

INTERVIEW	• Eligibility criteria • Medical history	• AD history • Prior/concomitant therapy
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS • Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI)	• Patient Oriented Eczema Measure (POEM) • Patient Global Impression of Severity (PGIS) • EuroQoL-5D-5L (EQ-5D-5L) • Scoring Atopic Dermatitis (SCORAD) subject-reported items
EXAM	• EASI • BSA • vIGA-AD • SCORAD investigator-reported items • Asthma Control Questionnaire-5 (ACQ-5) (if applicable)	• AE assessment • Vital signs • Physical examination • Hypersensitivity monitoring
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology • Clinical chemistry • Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides • Immunoglobulin (Ig)E levels • Blood samples for anti-drug antibody (ADA) and neutralizing antibody (nAb) assay	• Hypersensitivity testing (if applicable) • Optional biomarker samples: Whole blood (pharmacogenetic [PG]-DNA, transcriptomic PG-RNA, plasma, and serum); skin punch biopsy (lesional and non-lesional); skin tape harvest (lesional and non-lesional)
TREATMENT	• Randomization/drug assignment for Period A	• Administer study drug

WEEK 2 VISIT (± 3 Days):

INTERVIEW	• Prior/concomitant therapy	
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS	• PGIS • Patient Global Impression of Change (PGIC)
EXAM	• EASI • BSA • vIGA-AD	• AE assessment • Vital signs
CENTRAL LAB	• Hematology • Clinical chemistry	• Optional biomarker samples: Whole blood (PG-DNA [if not previously collected], PG-RNA, plasma, and serum)

WEEK 4 VISIT (± 3 Days):

INTERVIEW	• Prior/concomitant therapy	
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS • DLQI or CDLQI	• POEM • PGIS • PGIC • EQ-5D-5L • SCORAD subject-reported items
EXAM	• EASI • BSA • vIGA-AD • SCORAD investigator-reported items	• AE assessment • Vital signs • Hypersensitivity monitoring
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology • Clinical chemistry • Blood samples for ADA and nAb assay • Blood samples for pharmacokinetic (PK) assay • Hypersensitivity testing (if applicable)	• Optional biomarker samples: Whole blood (PG-DNA [if not previously collected], PG-RNA, plasma, and serum); skin punch biopsy (lesional); skin tape harvest (lesional)
TREATMENT	• Administer study drug	

WEEK 10 VISIT (± 3 Days):

INTERVIEW	• Prior/concomitant therapy	
PRO	• Worst Pruritus NRS • ADerm-SS	• ADerm-IS • PGIS • PGIC
EXAM	• EASI • BSA • vIGA-AD • AE assessment	• Height, weight, and waist circumference (adolescents only) • Vital signs
CENTRAL LAB	• Hematology • Chemistry	• Blood samples for PK assay

WEEK 16 VISIT (± 3 Days):

INTERVIEW	• Prior/concomitant therapy	
PRO	• Collect handheld electronic PRO device • Worst Pruritus NRS • ADerm-SS • ADerm-IS	• DLQI or CDLQI • POEM • PGIS • PGIC • EQ-5D-5L • SCORAD subject-reported items
EXAM	• EASI • BSA • vIGA-AD • SCORAD investigator-reported items	• AE assessment • Vital signs • Hypersensitivity monitoring
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology • Clinical chemistry • IgE levels • Blood samples for ADA and nAb assay • Blood samples for PK assay • Hypersensitivity testing (if applicable)	• Optional biomarker samples: Whole blood (PG-DNA [if not previously collected], PG-RNA, plasma, and serum); skin punch biopsy (lesional and non-lesional); skin tape harvest (lesional and non-lesional)
TREATMENT	• Randomization/drug assignment for Period B (placebo subjects only)	• Administer study drug

WEEK 20 VISIT (± 7 Days):

INTERVIEW	• Prior/concomitant therapy	
EXAM	• EASI • BSA • vIGA-AD	• Vital signs • AE assessment
CENTRAL LAB	• Hematology	• Clinical chemistry

WEEK 24 VISIT (± 7 Days):

INTERVIEW	• Prior/concomitant therapy	
EXAM	• EASI • BSA • vIGA-AD	• AE assessment

WEEK 28 VISIT (± 7 Days):

INTERVIEW	• Prior/concomitant therapy	
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS • DLQI or CDLQI • POEM	• PGIS • PGIC • EQ-5D-5L • SCORAD subject-reported items
EXAM	• EASI • BSA • vIGA-AD • SCORAD investigator-reported items	• AE assessment • Height, weight, and waist circumference (adolescents only) • Vital signs • Hypersensitivity monitoring
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology • Clinical chemistry	• Hypersensitivity testing (if applicable)
TREATMENT	• Administer study drug	

WEEK 40 VISIT (± 7 Days):

INTERVIEW	• Prior/concomitant therapy	
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS • DLQI or CDLQI	• POEM • PGIS • PGIC
EXAM	• EASI • BSA • vIGA-AD	• AE assessment • Vital signs • Hypersensitivity monitoring
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology • Clinical chemistry	• Hypersensitivity testing (if applicable)
TREATMENT	• Administer study drug	

2.2 Individual Post-Treatment Period Visit Activities

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

Activities are grouped by category (e.g., interview, exam, etc.). Further information about the activities is presented in Section 3.

Subjects who prematurely discontinue study drug should complete the Study Drug Discontinuation electronic case report form (eCRF) as part of the Premature Discontinuation (PD) Visit.

WEEK 52 (± 7 Days)/Premature Discontinuation:

INTERVIEW	• Prior/concomitant therapy	• TB screening (only for subjects with no prior documented positive TB test)
PRO	• Worst Pruritus NRS • ADerm-SS • ADerm-IS • DLQI or CDLQI • POEM	• PGIS • PGIC • EQ-5D-5L • SCORAD subject-reported items
EXAM	• EASI • BSA • vIGA-AD • SCORAD investigator-reported items • AE assessment	• 12-lead ECG • Weight and waist circumference (adults only) • Height, weight, and waist circumference (adolescents only) • Vital signs • Physical examination
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology • Clinical chemistry • TB test • IgE levels • Blood samples for ADA and nAb assay • Blood samples for PK assay	• Optional biomarker samples: Whole blood (PG-DNA [if not previously collected], PG-RNA, plasma, and serum); skin punch biopsy (lesional); skin tape harvest (lesional)

Follow-Up Call (20 Weeks After Last Study Drug Dose):

INTERVIEW	• Prior/concomitant therapy	• AE assessment

2.3 COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the Coronavirus Disease – 2019 (COVID-19) pandemic, if it is not possible for all study visits or procedures to be performed as specified due to travel restrictions or other reasons, Table 1 summarizes the modifications allowed per the scenario. If a subject does not meet any of the scenarios described below, contact the sponsor for further guidance.

Table 1. Modifications to Study Visits Due to COVID-19 Pandemic

Scenario	Actions
If the subject can come to the study site	Perform the study visit procedures and study drug administration as planned. If laboratory samples cannot be shipped to the central laboratory, a local laboratory may be used for routine assessment. Biomarker, PK, ADA, and nAb samples, if applicable, must still be shipped to the central laboratory. Local laboratory results should be reviewed by the Investigator as soon as possible. Local labs should be added to the Unscheduled local lab eCRF (see Section 3.12).
If the subject can come to the study site but a complete visit is not possible	Complete as many of the study procedures as possible as indicated in the planned study visit in Section 2.1.
For subjects who are not suspected or confirmed to have COVID-19, but are unable to attend an onsite visit (e.g., travel restrictions, quarantine)	1. Follow the quarantine and travel restrictions as dictated by local health authority. 2. Determine if the subject can perform an out of window (OOW) onsite visit (see Section 3.17). The study visits as described in the protocol should be conducted as close as possible to the scheduled study visit date. 3. Regardless of whether an onsite OOW visit can occur, a phone call from the site to the subject should be completed as close as possible to the date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete any ePRO assessment by interview (see Section 3.4). 4. If the visit is a dosing visit, an at-home visit is allowed to conduct study assessments and administer study drug (see Section 3.11). Remote/virtual EASI and vIGA-AD assessments are prohibited.
For subjects who are well but have been quarantined due to exposure to a confirmed case of COVID-19	1. Follow the quarantine and travel restrictions as dictated by local health authority. 2. Determine if the subject can perform an out of window (OOW) onsite visit (see Section 3.17). The study visits as described in the protocol should be conducted as close as possible to the scheduled study visit date. 3. Regardless of whether an onsite OOW visit can occur, a phone call from the site to the subject should be completed as close as possible to the date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete any ePRO assessment by interview (see Section 3.4).

Scenario	Actions
For subjects who have suspected or confirmed coronavirus disease (COVID-19)	1. Study drug should not be administered while the subject has COVID-19. 2. Study drug administration may resume after discussion with the TA MD. 3. Determine if the subject can perform an out of window (OOW) onsite visit (see Section 3.17). The study visits as described in the protocol should be conducted as close as possible to the scheduled study visit date. 4. Regardless of whether an onsite OOW visit can occur, a phone call from the site to the subject should be completed as close as possible to the date of the study visit. The phone call will query for any AEs and review concomitant medications. If possible, complete any ePRO assessment by interview (see Section 3.4). 5. Notify AbbVie of any subjects who are affected by this situation.

ADA = anti-drug antibody; COVID-19 = coronavirus disease – 2019; EASI = Eczema Area and Severity Index; ePRO = electronic patient-reported outcome; nAb = neutralizing antibody; OOW = out of window; PK = pharmacokinetic; TA MD = Therapeutic Area Medical Director; vIGA-AD = Validated Investigator Global Assessment scale for Atopic Dermatitis

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A signed assent should also be obtained at the same time for any adolescent subjects between 12 and 18 years of age who are participating in the study, where locally permissible and approved. A copy of the signed informed consent (and assent, if applicable) 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 (and assent, if applicable) 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 blood and/or skin biomarker research samples will only be collected if the subject or their legally authorized representative has voluntarily signed and dated a written consent form and assent, as applicable, describing the research. The written consent may be part of the main consent form. If the subject or their legally authorized representative does not consent to providing optional samples, the subject will still be allowed to participate in the study. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated before subject withdrawal of consent will remain part of the study results.

Due to the COVID-19 pandemic, 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.

3.2 Medical History

A complete medical history including demographics; history of AD; previous Hepatitis B vaccination; and history of tobacco (including e-cigarettes), alcohol, and drug use will be taken at Screening. The subject's medical history will be updated at the Baseline/Study Day 0 visit, including asthma symptoms (if applicable, using the ACQ-5, see Appendix B), prior to administration of the first dose of study drug. This updated medical history will serve as the baseline for clinical assessment.

3.3 Adverse Event Assessment

Please refer to Section 4.2.

In the event that an enrolled subject experiences an AE related to asthma, additional information will be collected utilizing a supplemental asthma CRF.

3.4 Patient-Reported Outcomes

Data Collection

Subjects will complete self-administered patient-reported outcome (PRO) instruments. Subjects should be instructed to follow the instructions provided with the instrument(s) 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. Site personnel will encourage completion of the instrument(s) at all specified visits and will ensure that a response is entered for all items.

PRO instruments that are administered at the site should be completed prior to drug administration and prior to any discussion of adverse events or any review of laboratory findings. The subject should

complete questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

Daily Worst Pruritus NRS, daily and weekly ADerm-SS, and daily and weekly ADerm-IS ePROs will be collected from subjects electronically every evening using a handheld device provided to the subject at Screening (see Section 3.10). The handheld electronic device will be programmed to allow data entry only once per day. All data entered on the device will be immediately stored to the device itself, as well as automatically uploaded to a central server. Data from the DLQI, CDLQI, POEM, PGIS, PGIC, SCORAD (subject-reported items), and EQ-5D-5L assessments will be collected electronically at the visits specified in Section 2.1. Subjects will use a tablet device at the site to enter the required pieces of information. Starting at the Week 16 visit, Daily Worst Pruritus NRS, ADerm-SS, and ADerm-IS ePROs will also be collected electronically at the prescribed visits. The electronic tablet device will be programmed to allow data entry for only the visits specified in the protocol and will not allow subjects to complete more than one of the same assessment at any one visit. All data entered on the handheld and electronic tablet devices will be immediately stored to the devices themselves and automatically uploaded to a central server.

Data stored on the central server will be considered source. The investigator and delegated staff will be able to access uploaded subject-entered data via a password protected website until the generation, receipt, and confirmation of the study archive. Data from the ePRO system will be archived and provided to the investigator at that time as a durable record of the site's ePRO data.

Worst Pruritus Numerical Rating Scale

The Worst Pruritus NRS (Appendix C) is an assessment tool used by subjects to report the intensity of pruritus during a 24-hour recall period. Subjects are asked to rate their pruritus at its worst during the past 24 hours on a scale of 0 to 10, with 0 being no itch and 10 being the worst imaginable itch.

Atopic Dermatitis Symptoms Scale

The ADerm-SS (Appendix D) is an 11-item questionnaire that assesses signs and symptoms subjects may experience due to AD. The ADerm-SS includes 3 items that subjects complete daily and 8 items that subjects complete each week, both using a 24-hour recall period. The 3 daily items include worst itch during sleep hours, worst itch during waking hours, and worst skin pain. The 8 weekly items include worst skin cracking, worst pain caused by skin cracking, worst dry skin, worst skin flaking, worst rash (i.e., redness, blisters, bumpy skin), worst skin thickening, worst bleeding, and worst skin oozing. All items of the ADerm-SS are scored on an 11-point NRS ranging from 0 (no [sign/symptom concept]) to 10 (worst possible [sign/symptom concept]). The psychometric properties of the ADerm-SS are being evaluated to establish its validity in assessing AD symptoms.

Atopic Dermatitis Impact Scale

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

SCORing Atopic Dermatitis – Subject-Reported Items

The SCORAD© (Appendix F) is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD. The assessment consists of 3 components: A = extent or affected body surface area, B = severity, and C = subjective symptoms. Component C will be completed by subjects in this study. Subjective assessment of itch and sleeplessness is recorded for each symptom by the subject or relative on a Visual Analog Scale (VAS) on the electronic tablet, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20.

Dermatology Life Quality Index

The DLQI (Appendix G) is a 10-item validated questionnaire used to assess the impact of AD disease symptoms and treatment on quality of life (QoL). It consists of 10 questions evaluating impact of skin diseases on different aspects of a subject's QoL over the prior week, including symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment. Each item is scored on a 4-point scale (0 = not at all/not relevant; 1 = a little; 2 = a lot; and 3 = very much). Item scores are added to provide a total score, ranging from 0 to 30, with higher scores indicating greater impairment of QoL. For general inflammatory skin conditions, a change in DLQI score of at least 4 points is considered the minimum clinically important difference (MCID). In this study, the DLQI will be administered to subjects who are ≥ 16 years old at the Baseline visit.

Children's Dermatology Life Quality Index

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

the CDLQI will be administered to subjects who are < 16 years old at the Baseline visit and will continue to be administered to these subjects for the duration of this study.

Patient Oriented Eczema Measure

The POEM (Appendix I) is a 7-item validated questionnaire used to assess disease symptoms in both children and adults. Subjects respond to 7 items, including dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping, with each item scored on a 5-point scale based on frequency (0 = no days; 1 = 1 to 2 days; 2 = 3 to 4 days; 3 = 5 to 6 days; and 4 = all days). Item scores (0 to 4) are added to provide a total score, ranging from 0 to 28, with the total score reflecting disease-related morbidity. A change in POEM score of 3.4 points is considered the MCID.

Patient Global Impression of Severity

The PGIS (Appendix J) is a single-question assessment in which subjects describe the severity of their AD symptoms at the present moment. Subjects rate their AD symptoms on a 7-point scale, ranging from 0 (Absent, no symptoms) to 6 (Very Severe, cannot be ignored and markedly limits daily activities).

Patient Global Impression of Change

The PGIC (Appendix K) is a single-question assessment in which subjects rate the overall change in their AD symptoms by comparing the severity of their symptoms at the present moment with the severity of their symptoms before they began study treatment. Subjects are asked to rate the overall change in their AD symptoms, with responses ranging from 1 ("Very much improved") to 7 ("Very much worse").

EuroQoL EQ-5D-5L

The EQ-5D-5L (Appendix L) is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-5L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 5 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate VAS.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If electronic PRO instruments (ePROs) cannot be completed on the tablet, they are permitted to be completed via phone or video interview.

Site staff will record the subject's responses on the screen shot of the PRO in the subject's language. The date, time, and interviewer name should be recorded in the source document. The investigator or study coordinator must transcribe the PRO responses into the TrialManager website. No other site roles will receive access to enter data into TrialManager. Training will be required for investigator data entry into TrialManager and will be provided upon request of the sponsor.

If appropriate site personnel can travel to the subject's home, the ePRO tablet can be taken to the subject's home for ePRO completion. All ePROs should be completed for the assigned visit.

3.5 Investigator Assessments

Investigator assessments will be recorded on source documents and then entered into the eCRF and conducted at the study visits specified in Section 2. Assessments should be performed by the investigator or qualified site personnel. To minimize variability, the same assessor should evaluate the subject at each visit for the duration of the study. Any assessor must be competent in performing such assessments. It is the responsibility of the site primary investigator to ensure that all assessors are qualified and trained to perform assessments and that all training is documented. If the same assessor is not available, the pre-identified back-up assessor should perform such assessments.

Eczema Area and Severity Index

The EASI (Appendix M) is a tool used to measure the extent (area) and severity of atopic eczema in 4 regions of the body (head and neck; trunk, including lower extremities; upper limbs; and lower limbs). An area score and a severity score are determined for each of the 4 regions. Each region's area score and severity score are multiplied together and then by a multiplier. The total scores from each region are added together to determine the final EASI score. Grades for dryness or scaling are not assessed by the EASI score.

Body Surface Area

A clinical estimation is made of the total BSA affected by AD. The surface area of the subject's right or left hand is designated as the measuring device, with the total surface of the palm and 5 digits assumed to be approximately equivalent to 1% of the subject's total BSA.

Validated Investigator Global Assessment Scale for Atopic Dermatitis

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

SCORing Atopic Dermatitis

Study investigators will complete Components A and B of the SCORAD assessment (Appendix F) previously described. The extent of AD (Component A) is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100%. Component B is the assessment of the severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points). The SCORAD is calculated using the formula A/5 + 7B/2 + C (from the subject assessment), and the maximum score is 103. SCORAD Components A and B will not be on the electronic tablet; instead, they will be performed on paper worksheets and manually entered

into the eCRF. The rule of 9's method should be used to assess the percentage of each defined body area on the paper worksheets for Component A.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Collection of investigator assessment data is not permitted by remote or virtual visits.

3.6 12-Lead Electrocardiogram

A 12-lead ECG will be performed at designated study visits specified in Section 2. The ECG should be performed prior to blood collection.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol-required documentation is available and nothing has changed in the subject's health status since the time of the test that warrants a repeat test.

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

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

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

3.7 Height, Weight, and Waist Circumference

For the adult population, height will be measured at Screening only with shoes off. Body weight will be measured at scheduled visits specified in Section 2. The subject should wear lightweight clothing and no shoes during weighing. Waist circumference should be measured at Screening and Week 52; however, if missed at Screening it can be recorded at the Baseline (Study Day 0) visit.

For the adolescent population (as defined at Baseline), height, body weight, and waist circumference will be measured at Screening (however, if missed at Screening it can be recorded at the Baseline [Study Day 0]), Week 10, Week 28, and Week 52 with shoes off. The subject should wear lightweight clothing and no shoes during weighing.

3.8 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure (BP), pulse rate, respiratory rate, and body temperature will be obtained at visits specified in Section 2. BP and pulse rate should be measured after the subject has been sitting for at least 3 minutes and before blood draws are performed.

3.9 Physical Examination

A complete physical examination will be performed at the designated study visits specified in Section 2. The physical examination performed on Study Day 0 will serve as the baseline physical examination for the entire study. If appropriate, a targeted physical exam should be performed at any other visit (e.g., to evaluate a reported adverse event). Any significant physical examination findings after the first dose will be recorded as AEs, while any findings prior to the first dose will be recorded as medical history. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

3.10 Handheld ePRO Device

During the Screening Visit, subjects will be dispensed a handheld ePRO device to collect daily Worst Pruritus NRS, daily and weekly ADerm-SS, and daily and weekly ADerm-IS information. At each visit, site representatives should check to see that subjects have performed the required assessments between study visits. Data will be collected from the day of the Screening visit through the Week 16 visit.

3.11 Study Drug Administration

Study drug will be administered to subjects beginning at Baseline (Study Day 0) and as specified in Section 2.1. All subcutaneous (SC) doses of risankizumab and placebo will be administered by study site personnel under the direction of the investigator. The date and time (to the nearest minute) of onset of study drug administration will be recorded in the subject's medical record. The first dose of study drug will be administered after all other Baseline (Study Day 0) procedures are completed.

Study drug administration instructions for risankizumab pre-filled syringes will be provided for use by site staff.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If a subject cannot travel to the site for a visit when study drug administration is planned, site personnel may travel to the subject's home to conduct an at-home visit. Study drug may be transported under

appropriate storage conditions and administered by trained site personnel. The site must contact the sponsor to obtain instructions on how to dispense drug in the IRT system for at-home visits.

If an at-home visit is scheduled, site staff should also bring the ePRO tablet to the home for the subject to complete those assessments, see Section 3.4 for more details.

Monitoring for Hypersensitivity Reactions

Therapeutic protein products, such as biologics, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions that have often been grouped as "infusion or injection reactions" in the past. Although the term implies a certain temporal relationship, infusion or injection reactions are otherwise not well defined and may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to antibody responses, such as cytokine release syndrome.

In the event of a suspected systemic hypersensitivity/anaphylactic reaction, in addition to the standard AE eCRF, a supplemental Hypersensitivity Reactions eCRF should also be completed by the site. The clinical criterion for diagnosing anaphylaxis is provided in Appendix O for reference; symptoms of anaphylactic reaction usually occur within 24 hours after exposure to an allergen. These are guidelines that are used to help diagnose anaphylaxis. The investigator is encouraged to report any suspected reactions.

Subjects should be closely monitored for signs and symptoms of hypersensitivity reactions, including allergic reactions and anaphylaxis, for approximately 2 hours after study drug administration at the Baseline/Study Day 0 and Week 16 visits, and 1 hour after all other doses of study drug (dosing visits other than the Study Day 0 and Week 16 visits). A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the injections.

All appropriate medical support measures (e.g., diphenhydramine, steroids, epinephrine, oxygen) for the treatment of suspected hypersensitivity reactions should be available for immediate use in the event that a suspected hypersensitivity reaction occurs. Subjects who manifest any new signs or symptoms during the injection should be monitored for appropriate resolution prior to leaving the site. Subjects are encouraged to report any symptoms related to a possible injection-related reactions or local injection site reaction or late phase reactions to the site any time during the study. A patient information card listing the symptoms of these reactions will be provided to the participants.

In the event of a suspected anaphylactic reaction, blood and serum samples should also be collected as described in Section 3.12.

3.12 Clinical Laboratory Tests

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. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

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

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; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

Clinical Laboratory Tests		
HEMATOLOGY	**CLINICAL CHEMISTRY**	**URINALYSIS**
Hematocrit Hemoglobin Red Blood Cell (RBC) count/ Erythrocytes Mean Corpuscular Volume (MCV) White Blood Cell (WBC) count/ Leukocytes Platelet count/Thrombocytes **Diff. Automatic (absolute count):** Neutrophils Eosinophils Basophils Monocytes Lymphocytes **Manual Differential (ONLY IF Automated Differential is abnormal):** Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear Eosinophils Basophils Monocytes Lymphocytes	**Electrolytes** Calcium Sodium Potassium Chloride Bicarbonate **Substrates** Glucose Blood urea nitrogen (BUN) Creatinine Estimated glomerular filtration rate (eGFR) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Albumin High-sensitivity C-Reactive Protein (hsCRP) Cholesterol, total[a] LDL Cholesterol[a] HDL Cholesterol[a] Triglycerides[a] FSH[b]	**Dipstick Urinalysis** Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocytes Urine WBC/Leukocytes Urine pH Urine creatinine **Urine Sediment** (microscopic examination, **only if** urine analysis abnormal) Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sediment Crystals, Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leukocytes **Urine** Urine Albumin-to-Creatinine Ratio (UACR)

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><td>Coagulation:
International Normalized Ratio (INR)[c]</td><td rowspan="2">Enzymes
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Alkaline Phosphatase (AP)
Gamma-glutamyl transferase (GGT/γ-GT)
Creatine Kinase (CK)
Only if CK is elevated:
Troponin (point-of-care) OR
Troponin (central lab) + CK-MB</td><td></td></tr>
<tr><td>INFECTION SCREENING</td><td>PREGNANCY TESTING[e]</td></tr>
<tr><td rowspan="5">Hepatitis B surface antigen (HBs Ag) (qualitative)[d]
Hepatitis B surface antibody (HBs Ab) (qualitative)[d]
Anti-Hepatitis B core (HBc) total (qualitative)[d]
Hepatitis B Virus (HBV) DNA (quantitative)[d]
Anti-Hepatitis C Virus (HCV) (qualitative)[d]
HCV RNA (quantitative)[d]
HIV 1 and HIV-2 Ab (qualitative)[d]
QuantiFERON®-TB (or Interferon gamma release assay [IGRA] equivalent) and/or purified protein derivative (PPD)</td><td rowspan="4">ADDITIONAL TESTING
IgE</td><td>Urine Pregnancy test (local)[f]
Serum Pregnancy test[g]</td></tr>
<tr><td>PK/IMMUNOGENICITY</td></tr>
<tr><td>Serum risankizumab concentration
Serum ADA
Serum nAb</td></tr>
<tr><td>ANAPHYLAXIS TESTING[h]</td></tr>
<tr><td>Serum risankizumab concentration[i]
ADA[i]
nAb[i]
Tryptase[j]
Histamine</td></tr>
</table>

a. Performed only at Baseline visit (following a minimum 8-hour fast).

b. FSH testing is to be done at Screening in all women aged ≤ 55 years with no menses for 12 or more months without an alternative medical cause.

c. INR test only performed if ALT or AST > 3 × ULN (upper limit of normal).

d. Performed only at Screening.

e. Pregnancy testing is not required for female subjects of non-childbearing potential (defined in protocol).

f. Urine pregnancy test will be performed at every dosing visit and the Week 52/PD Visit and must be conducted prior to study drug dosing. Negative urine pregnancy test results must be confirmed prior to study drug dosing.

g. Serum pregnancy test is conducted at Screening and at other visits only if urine pregnancy test is positive. Negative serum pregnancy test results must be confirmed prior to study drug dosing.

h. Only performed in case of a suspected anaphylactic reaction.

i. PK and ADA/nAb samples drawn in context of a suspected anaphylactic reaction are collected in addition to those collected at scheduled time points for PK/immunogenicity and are only collected if a suspected anaphylactic reaction occurs while at the study site.

j. A follow-up tryptase level should be collected a minimum of 2 weeks after any suspected anaphylaxis event.

Pregnancy Tests (Serum and Urine)

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Pregnancy testing should not be performed for postmenopausal women.

A serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at Baseline for all female subjects. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the study;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Additional urine pregnancy tests for female subjects of childbearing potential will be performed at visits indicated in Section 2. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

If the urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If the urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study.

Follicle-Stimulating Hormone (FSH)

Follicle-stimulating hormone (FSH) should be tested at Screening if the female subject is ≤ 55 years of age AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization.

Clinical Chemistry

Blood samples will be collected following a minimum 8-hour fast for the Baseline visit (i.e., for lipid testing). If a subject is not able to fast at this visit, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation and lab requisition. Blood samples at other visits can be drawn without prior fast.

Urinalysis

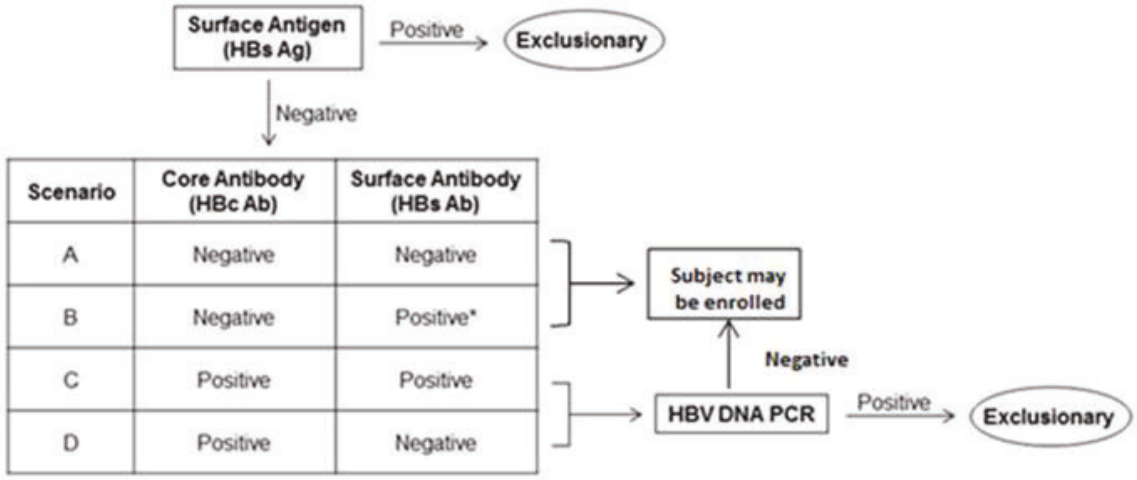
Dipstick urinalysis will be completed by the central laboratory at the Screening visit. Specified abnormal macroscopic urinalyses, defined as leukocytes, nitrite, protein, ketones, blood greater than negative, or glucose greater than normal, will be followed-up with a microscopic analysis at the central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

Hepatitis B and C Testing

All subjects will be tested for the presence of the Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) at Screening. Subjects with Hepatitis B (HBs Ag positive [+] or detected sensitivity on the HBV DNA PCR qualitative test) or Hepatitis C (HCV RNA detectable in any subject with anti-HCV Ab) will be excluded. Subjects who have been vaccinated against Hepatitis B and are HBs Ab positive may be enrolled. If HBs Ag is negative but Hepatitis B core antibodies total is positive, Hepatitis B virus DNA will be quantified. If Hepatitis B virus DNA level is undetectable at Screening, the subject can participate in this study. If Hepatitis C virus antibodies level is positive, Hepatitis C virus RNA will be quantified. If Hepatitis C RNA level is undetectable at Screening, the subject can participate in this study.

Where mandated by local requirements; subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening should have HBV DNA PCR testing performed every 12 weeks (q12w). HBV DNA PCR testing q12w is not necessary when the subject has a history of HBV vaccine and is HBs Ab+ and HBc Ab–.

Figure 1. Interpretation and Management of HBV Serologic Test Results



DNA = deoxyribonucleic acid; HBs Ag = hepatitis B surface antigen; HBs Ag = hepatitis B surface antigen; HBV = hepatitis C virus; PCR = polymerase chain reaction

* A positive test result for HBs Ab is expected for subjects who have had a HBV vaccination. For subjects without a history of HBV vaccination (and where mandated by local requirements), a positive result for HBs Ab requires HBV DNA PCR testing.

HIV Testing

HIV testing will be performed at Screening. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study

participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

TB Screening

Subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or IGRA equivalent) or a TB Skin Test (PPD) at the Screening visit and at Week 52, as specified in the study activity table.

At Screening, all subjects will be assessed for evidence of TB, and if positive, additional risk factors will be evaluated. If a subject had a negative PPD test or QuantiFERON-TB Gold Test (or IGRA equivalent) within 90 days prior to Screening and all protocol-required documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. Subjects who have tested positive will not have another test performed.

At Week 52, subjects with no prior positive TB test will be tested for TB by either the QuantiFERON-TB Gold Test (or IGRA equivalent) or a TB Skin Test (PPD).

The QuantiFERON®-TB Gold assay test will be supplied and analyzed by the central laboratory. (QuantiFERON-TB test is preferred over TB Skin Test.) Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

- If the **QuantiFERON-TB Gold Test (or IGRA equivalent) is NOT possible** (or if both the QuantiFERON-TB Gold Test [or IGRA equivalent] and the PPD Skin Test are required per local guidelines), the PPD Skin Test will be performed according to standard clinical practice.
    - The PPD Skin Test 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."
- If subject had a positive QuantiFERON-TB Gold (or IGRA equivalent) or PPD test at Screening, the test should not be repeated. Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.
- If the **TB screening test** (either PPD or the QuantiFERON-TB Gold test [or IGRA equivalent]) **is positive, or** if there is a **repeat indeterminate** QuantiFERON-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate in the study if **further work-up** (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB.
- If the subject is diagnosed with **active TB**, the subject should not be randomized in the study and should not receive study drug. Subject will be considered as a **screening failure**.

- If presence of **latent TB** is established, subjects are not required to be treated with prophylactic anti-TB therapy prior to or during the study, if considered low risk for reactivation per investigator judgment.
- If the subject is diagnosed with **active TB** after being randomized, the subject should not receive any further study drug and follow the PD Visit procedure (Section 2.2).
- If **TB (latent or active)** is diagnosed during the study, it is also necessary to report it as an AE in the source documents and eCRFs. In the case of a TB-related AE, a TB supplemental form that provides additional information will be completed by the investigator or designee.

Hypersensitivity/Anaphylaxis Testing

Anaphylaxis testing is only performed in case of a suspected anaphylactic reaction. Samples should be collected as follows:

Plasma tryptase: Optimally, measurement needs to be obtained from 15 minutes to 3 hours of symptom onset, but no later than 6 hours after (tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours);-a follow-up tryptase level should be collected a minimum of 2 weeks after any suspected anaphylaxis event.

Plasma histamine: Blood samples for measurement of histamine levels are optimally obtained 5 - 15 minutes after symptom onset and no later than 1 hour.

If a suspected systemic hypersensitivity reaction occurs on site, in addition to tryptase and histamine levels, PK and ADA/nAb samples will also be collected.

In the event that a serious systemic hypersensitivity reaction such as anaphylaxis occurs while the subject is not on site at the study clinic, please advise the treating facility to obtain tryptase and histamine levels to help better understand and characterize the diagnosis.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.

3.13 Drug Concentration and Anti-Drug Antibody Measurements

Blood samples for PK, ADA, and nAb assays should be collected within 60 minutes prior to dose administration at dosing visits. For subjects who prematurely discontinue from study drug treatment, PK and ADA samples will be collected at any time during the PD Visit.

Collection of Blood Samples for Risankizumab Analysis, ADA Assay, and nAb Assay

Blood samples for analysis of risankizumab serum concentrations, ADA assay, and nAB assay will be collected throughout the treatment period on the study days specified in the protocol. Samples will be collected by venipuncture into appropriately-labeled, evacuated serum collection tubes. The time that each blood sample (PK and ADA/nAb) is collected will be recorded to the nearest minute in the source document.

Measurement Methods

Serum concentrations of risankizumab and ADA and nAb assessments will be done using validated methods at or under the supervision of the Bioanalysis Department at AbbVie. The presence of ADA to risankizumab will be assessed via a tiered approach with an electrochemiluminescence assay using screening, confirmatory, and titration analyses. Samples that are confirmed positive may be further characterized in a validated nAb assay. Any additional analytes may be analyzed using nonvalidated methods. Serum samples collected for risankizumab PK and ADA analysis may be used for future assay development or validation activities.

Disposition of Samples

The frozen serum samples for risankizumab analysis and ADA and nAb assays will be packed in dry ice sufficient to last during transportation and shipped from the study site to the central lab according to instructions from AbbVie.

3.14 Biomarker and/or Exploratory Research Sampling

Optional whole blood, biopsy, and skin tape samples will be collected for biomarker research at study visits outlined in Section 2 above. All biomarker samples should be collected, 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 risankizumab (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.

Skin Punch Biopsy and Tape Harvest Samples

Skin punch biopsy and skin tape harvest samples will be obtained for investigations including, but not limited to epigenetics, transcriptomics, proteomics, IHC and targeted investigations.

For subjects who consent, both lesional and non-lesional skin punch biopsies and tape strip samples will be collected during the study. Lesional skin punch biopsies and tape strip samples should be collected at the Baseline, Week 4, Week 16, and Week 52/PD visits. In addition, non-lesional skin punch biopsies and tape strip samples should also be collected at the Baseline and Week 16 visits. Suitable sites for skin biopsy will include any cutaneous surface except the head and neck, genitals, hands, feet, elbows, lower leg, or knees. The lesional biopsy should be taken from a target lesion initially and always taken from the same lesion or comparable lesion thereafter. The non-lesional sample should be collected from the most normal appearing skin in a relative proximity to the lesional skin biopsy site (i.e., same anatomical area), at least 5 cm away from the lesion. It is recommended to photograph the location from which the biopsies will be collected and document it on a diagram. These photographs are to be used only by the sites to identify biopsy location for subsequent visits.

Skin tape harvest samples will be taken prior to the punch biopsy and from a site adjacent to the site used for skin punch biopsies. Sites should not biopsy over the taping site. Patches will be applied to the skin briefly and then removed. Each sample will consist of 20 discs applied to the same exact area in succession. Skin tape harvest samples should be taken from the same lesional and non-lesional areas for each visit.

3.15 Subject Withdrawal from Study

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

3.16 Unscheduled Visits

An unscheduled visit should be performed when the subjects comes in for a medical visit for safety evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3.12, or for other tests, at the investigator's discretion. No efficacy assessments and no drug administration should be performed at this visit.

Visits for dispensing new study drug in case of temperature excursion, loss, or damage are not considered Unscheduled Visits. In addition, visits to only retest a lab will not be considered an Unscheduled Visit.

3.17 Out of Window Visits Due to COVID-19 Pandemic

If a visit can be performed onsite by OOW, consult with the sponsor to determine if the OOW visit is permitted.

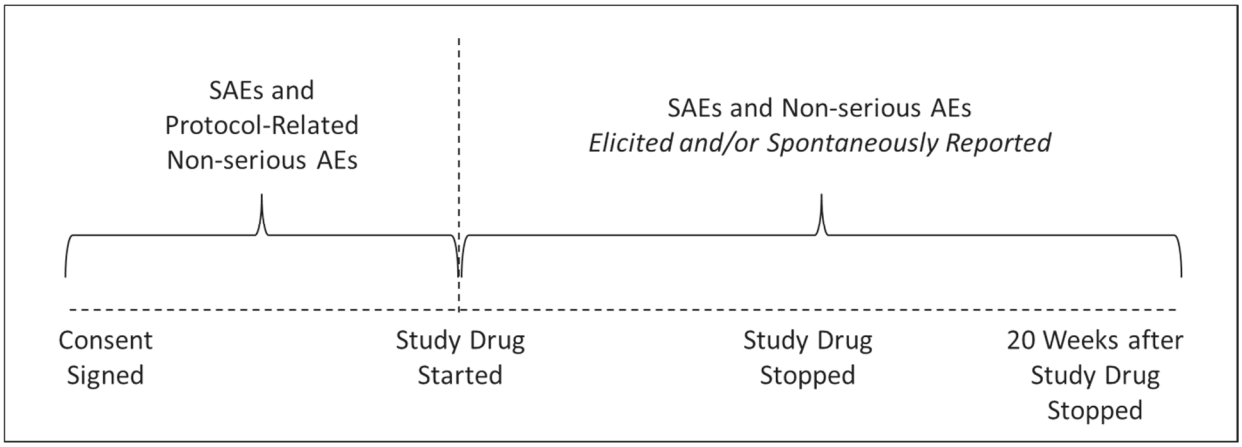
Regardless of whether an onsite OOW visit can occur, a phone call from the site to the enrolled subject should be conducted as close to the date of the study visit as possible to query for any AEs and to review concomitant medications.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious adverse events (SAEs), as well as protocol-related non-serious AEs (e.g., bruising related to blood draw), will be collected from the time the subject signs the study-specific informed consent until study drug administration. From the time of study drug administration until 140 days following discontinuation of study treatment has elapsed, all AEs and SAEs will be collected, whether solicited or spontaneously reported by the subject.

Figure 2. Safety Assessment



4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (TEAEs) (i.e., any event that begins or worsens in severity after initiation of study drug through 140 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 for the severity grade table and the most related for 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.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-case report form (CRF) 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
AbbVie
Dept. R48S, Bldg. AP31-2
1 North Waukegan Road
North Chicago, Illinois 60064
Phone: +1 (847) 938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

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

Contact Information:

Phone: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director 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 Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

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

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

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

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

4.4 Reporting Product Complaints

Product complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 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's Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a Development Safety Update Report (DSUR) reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

5.2 Additional Country-Specific Requirements – Japan

For Japanese sites, the following country-specific requirements are applicable:

- Protocol Section 5.1, Eligibility Criterion 2: Subjects under 20 years of age must voluntarily sign and date an informed consent, in addition to their parent or legal guardian.
- Protocol Section 5.9: In addition to the other responsibilities listed, investigators are also responsible for recording protocol deviations in the appropriate source records.

6 STUDY DRUG

6.1 Treatments Administered

Study drug will be administered by a healthcare professional in the form of a SC injection at the visits listed in Section 2.1. For additional details on dispensing study drug in the event of home administration due to the COVID-19 pandemic, see Section 3.11.

Risankizumab and matching placebo will be provided by AbbVie as a solution for injection in a pre-filled syringe (PFS).

Study site staff will administer study drug as follows:

- Risankizumab 150 mg: Two SC injections of 75 mg and 2 SC injections of placebo at Baseline (Study Day 0), Week 4, Week 16, Week 28, and Week 40.
- Risankizumab 300 mg: Four SC injections of 75 mg at Baseline (Study Day 0), Week 4, Week 16, Week 28, and Week 40.
- Placebo: Four SC injections at Baseline (Study Day 0) and at Week 4. At Week 16, subjects are re-randomized to receive either risankizumab 150 mg or 300 mg for the remainder of the study at Week 16, Week 28, and Week 40. Study drug will be administered as described above.

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. Visit date information and study drug return information for each kit will be available through the IRT system.

6.2 Packaging and Labeling

Study drug packaged in 75 mg PFS will be provided in a blinded fashion and packaged in cartons containing 1 syringe per carton. Each kit will be labeled as required per local requirements. Each kit label will contain a unique kit number. This kit number is assigned to a subject via the IRT and encodes the appropriate study drug to be administered at the subjects corresponding study visit.

All labels must remain affixed to the study drug at all times and should never be removed for any reason. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Risankizumab and matching placebo kits must be kept protected from light in the original packaging, in a refrigerator between 2°C to 8°C (36°F to 46°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study

must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

The refrigerator temperature must be recorded each business day. Malfunctions or temperature excursions must be reported to the sponsor immediately upon notice. Study drug should be quarantined and not dispensed until AbbVie (or the AbbVie Temperature Excursion Management System) deems the drug as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use or are returned to AbbVie. Investigational products are for investigational use only and are to be used only within the context of this study.

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 2, randomized, double-blind, placebo-controlled multicenter study to evaluate the safety and efficacy of risankizumab in adult and adolescent subjects with a confirmed diagnosis of moderate to severe AD and onset of symptoms at least 2 years before the Baseline Visit. Subjects who meet eligibility criteria will be randomized in a 2:2:1 ratio to one of 3 treatment groups: (1) risankizumab 150 mg (62 subjects), (2) risankizumab 300 mg (62 subjects), or (3) matching placebo (31 subjects). Subjects in the placebo group will be re-randomized in a 1:1 ratio to receive either risankizumab 150 mg or 300 mg at Week 16.

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

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

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

6.4 Selection and Timing of Dose for Each Subject

During Period A, study site staff will administer study drug (risankizumab 150 mg, risankizumab 300 mg, or matching placebo) subcutaneously at the Baseline (Study Day 0) and Week 4 visits.

During Period B, study site staff will administer either risankizumab 150 mg or risankizumab 300 mg at the Week 16, Week 28, and Week 40 visits.

7 REFERENCES

1. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23-31.

2. Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11-8.

3. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACQ-5	Asthma Control Questionnaire-5
AD	Atopic dermatitis
ADA	Anti-drug antibody
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CDLQI	Children's Dermatology Life Quality Index
CK	Creatine kinase
COVID-19	Coronavirus Disease - 2019
CRF	Case report form
DNA	Deoxyribonucleic acid
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQoL-5D-5L
FSH	Follicle-stimulating hormone
HBc	Hepatitis B core
HBs Ab	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
Ig	Immunoglobulin
IGRA	Interferon-gamma release assay
IMP	Investigational medical product
IRT	Interactive response technology
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibody
NRS	Numerical rating scale
OOW	Out of window
PCR	Polymerase chain reaction
PD	Premature discontinuation
PEF	Peak expiratory flow
PFS	Pre-filled syringe
PG	Pharmacogenetic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPD	Purified protein derivative
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality of life
RBC	Red blood cell
RSI	Reference Safety Information
SAE	Serious adverse event
SC	Subcutaneous(ly)
SCORAD	SCORing Atopic Dermatitis
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis

UACR	Urine albumin-to-creatinine ratio
VAS	Visual analog scale
vIGA-AD	Validated Investigator Global Assessment scale for Atopic Dermatitis
WBC	White blood cell

APPENDIX B. ACQ-5 EXAMPLE

ASTHMA CONTROL QUESTIONNAIRE©
(LANGUAGE VERSION FOR COUNTRY)

PATIENT ID: _____

DATE: _____

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

ACQ-5 - Canada/English - Mapi.
ACQ-5_AU1.0_eng-CAen.doc

APPENDIX C. WORST PRURITUS NRS EXAMPLE

Worst Pruritus Numeric Rating Scale

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

0	1	2	3	4	5	6	7	8	9	10
No Itch										Worst Imaginable Itch

Worst Pruritus NRS V1 © AbbVie 12-7-2017

APPENDIX D. ADERM-SS QUESTIONNAIRE EXAMPLE

Atopic Dermatitis Symptom Scale (ADerm-SS)

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

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

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

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

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

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

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

APPENDIX E. ADERM-IS QUESTIONNAIRE EXAMPLE

Atopic Dermatitis Impact Scale (ADerm-IS)

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

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

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

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

4. During the past seven days, how much did your AD **limit** your **household activities** (e.g., washing dishes, sweeping, doing laundry)?	Not limited … Extremely limited 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
5. During the past seven days, how much did your AD **limit** your **physical activities** (e.g., walking, exercising)?	Not limited … Extremely limited 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
6. During the past seven days, how much did your AD **limit** your **social activities**?	Not limited … Extremely limited 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
7. During the past seven days, how **difficult** was it for you **to concentrate** due to AD?	Not difficult … Extremely difficult 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8. During the past seven days, how **self-conscious** did you feel due to AD?	Not self-conscious … Extremely self-conscious 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
9. During the past seven days, how **embarrassed** did you feel due to AD?	Not embarrassed … Extremely embarrassed 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
10. During the past seven days, how **sad** did you feel due to AD?	Not sad … Extremely sad 0 1 2 3 4 5 6 7 8 9 10 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

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

APPENDIX F. SCORAD EXAMPLE

The SCORAD[1] is a tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD.

Body Area Affected:

The extent of AD is assessed as a percentage of each defined body area. To help in determining this extent, the sites affected by eczema are shaded on a drawing of a body. The rule of 9 is used to calculate the affected area as a percentage of the whole body:

- Head and neck 9%
- Upper limbs 9% each
- Lower limbs 18% each
- Anterior trunk 18%
- Back 18%
- Genitals 1%

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

Symptom Severity:

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

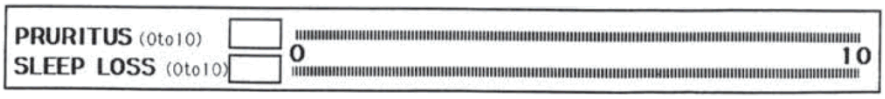
- Redness
- Swelling
- Oozing/crusting
- Scratch marks
- Skin thickening (lichenification)
- Dryness (this is assessed in an area where there is no inflammation)

The scores for these 6 specific symptoms should be added, for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation.

Subjective Symptoms:

Subjective assessment of itch and sleeplessness is recorded for each symptom by the subject on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation.

Visual analog scale (average for the last 3 days or nights)



(10 cm in length)

SCORAD Calculation:

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

APPENDIX G. DLQI QUESTIONNAIRE EXAMPLE

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score: ☐
Address: Diagnosis:

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

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

APPENDIX H. CDLQI QUESTIONNAIRE EXAMPLE

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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

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

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

7.	Last week, was it **school time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school	☐
			Very much	☐
			Quite a lot	☐
			Only a little	☐
			Not at all	☐
	OR			
	was it **holiday time?**	**If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much	☐
			Quite a lot	☐
			Only a little	☐
			Not at all	☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much	☐
			Quite a lot	☐
			Only a little	☐
			Not at all	☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much	☐
			Quite a lot	☐
			Only a little	☐
			Not at all	☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much	☐
			Quite a lot	☐
			Only a little	☐
			Not at all	☐

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

abbvie

APPENDIX I. POEM QUESTIONNAIRE EXAMPLE

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

Patient Details: _____

_____

_____

_____ Date: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

POEM for self-completion

How is the scoring done?

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

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

Note:

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

What does a poem score mean?

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

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

Do I need permission to use the scale?

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

References

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

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

APPENDIX J. PGIS QUESTIONNAIRE EXAMPLE

Seven point response scale

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

1. Right now, my atopic dermatitis (AD) symptoms are:

☐$_0$ **Absent:** No symptoms

☐$_1$ **Minimal:** Can be easily ignored without effort

☐$_2$ **Mild:** Can be ignored with effort

☐$_3$ **Moderate:** Cannot be ignored but does not influence my daily activities

☐$_4$ **Moderately severe:** Cannot be ignored and occasionally limits my daily activities

☐$_5$ **Severe:** Cannot be ignored and often limits my concentration on daily activities

☐$_6$ **Very severe:** Cannot be ignored and markedly limits my daily activities.

APPENDIX K. PGIC QUESTIONNAIRE EXAMPLE

Seven-point response scale

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

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

☐1	**Very much improved**
☐2	**Much improved**
☐3	**Minimally improved**
☐4	**No change**
☐5	**Minimally worse**
☐6	**Much worse**
☐7	**Very much worse**

APPENDIX L. EQ-5D-5L EXAMPLE

Under each heading, please check the ONE box that best describes your health TODAY:

Mobility

I have no problems walking ☐

I have slight problems walking ☐

I have moderate problems walking ☐

I have severe problems walking ☐

I am unable to walk ☐

Self-Care

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family, or leisure activities)

I have no problems with doing my usual activities ☐

I have slight problems with doing my usual activities ☐

I have moderate problems with doing my usual activities ☐

I have severe problems with doing my usual activities ☐

I am unable to do my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

I am slightly anxious or depressed ☐

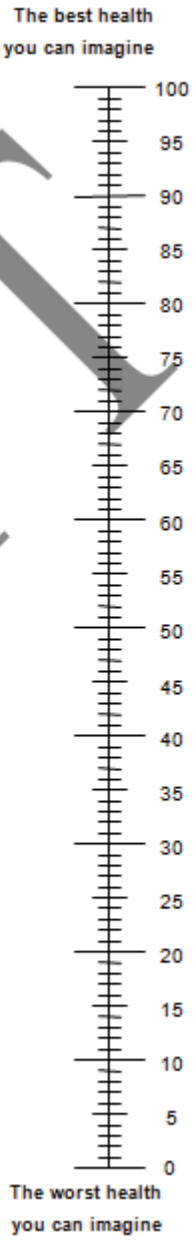
I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX M. EASI SCORING EXAMPLE

An EASI[2] score is a tool used to measure the extent (area) and severity of atopic eczema (Eczema Area and Severity Index). EASI score does not include a grade for dryness or scaling.

Assignments for the following body regions are as follows:

- Head and Neck
- Trunk: include with the lower extremities
- Upper limbs
- Lower limbs

Area Score

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

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

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

Severity Score

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

The four signs are:

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

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

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

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

0 = None, absent

1 = Mild

2 = Moderate

3 = Severe

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

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

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

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

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

APPENDIX N. VIGA-AD QUESTIONNAIRE EXAMPLE

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

SAMPLE

Instructions:

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

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

SAMPLE

Notes:

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

For example:

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

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

APPENDIX O. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis[3] is highly likely when any one of the following 3 criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

   b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that subject (minutes to several hours):

   a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

   * Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mg Hg from 11 to 17 years.

Serious Systemic Hypersensitivity Reaction: A hypersensitivity reaction is a clinical sign or symptom, or constellation of signs or symptoms, caused by an inappropriate and excessive immunologic reaction to study drug administration. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not occur at the local site of study drug administration (e.g., not an injection site reaction). A serious systemic hypersensitivity reaction is a systemic hypersensitivity reaction that fulfills criteria for a SAE.

In the event of an anaphylactic reaction, blood samples will be drawn per Section 3.12 after the onset of the reaction. Separate instructions for the collection, handling, storage, and shipping of these labs will be provided outside of the study protocol.