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Protocol for Study M23-696

Atopic Dermatitis: Comparison of Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Adult and Adolescent Subjects

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FULL TITLE: A Phase 3b/4 Randomized, Open-label, Efficacy Assessor Blinded Study, Comparing the Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Subjects with Moderate to Severe Atopic Dermatitis (Level-Up)

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

Sponsor contact for all non-emergency issues:

[redacted]
AbbVie
Avenida de Burgos, 91
28050 Madrid
Spain

Mobile: [redacted]
Email:

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Sponsor emergency medical contact:
[redacted] MD
[redacted] Global Medical Affairs
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Mobile:
Email: [redacted]

EMERGENCY 24 hour Number: +1 973-784-6402

For Non-EU Countries:
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
United States of America

For EU Countries:
AbbVie Deutschland GmbH & Co. KG (AbbVie)
Knollstrasse 50
67061 Ludwigshafen
Germany

* For European Union countries: the sponsor is AbbVie Deutschland GmbH & Co. KG. The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

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1 SYNOPSIS

Title: A Phase 3b/4 Randomized, Open-label, Efficacy Assessor Blinded Study, Comparing the Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Subjects with Moderate to Severe Atopic Dermatitis (Level-Up)	
Background and Rationale:	Upadacitinib is an oral, once-daily, selective, and reversible small-molecule JAK inhibitor, engineered to have greater inhibitory potency for JAK1 versus JAK2, JAK3, and tyrosine kinase 2 (TYK2). Janus kinase 1 inhibition blocks the signaling of many important pro-inflammatory cytokines, including interleukin (IL)-2, IL-6, IL-7, and IL-15, interferon (IFN)-γ, which are known contributors to inflammatory disorders. It also blocks the signaling of IL-4, IL-13, IL-31, IL-22, IFN-γ, thymic stromal lymphopoietin (TSLP) cytokines that play an important role in the pathogenesis of atopic dermatitis (AD). Upadacitinib has been approved in at least one country for the treatment of moderate to severe/active immune mediated inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, Crohn's disease, and AD. Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). Dupilumab has been approved in at least one country for the treatment of moderate to severe AD, moderate to severe asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis. This study aims to provide data on the efficacy and safety of upadacitinib initiated at 15 mg QD and dose escalated based on the clinical response, compared with dupilumab as per its label, after 16 weeks of treatment.
Objective(s) and Endpoint(s):	**Primary Objective** The primary study objective, related to Study Period 1, is to assess the efficacy and safety of upadacitinib, initiated at 15 mg once daily (QD) and dose adjusted based on clinical response, compared with dupilumab as per its label. An additional objective, related to Study Period 2, is to assess the efficacy and safety of upadacitinib, initiated at 15 mg QD, and dose adjusted based on clinical response, in subjects with inadequate response to dupilumab. The primary efficacy objective is based on the achievement of a composite endpoint of at least a 90% reduction in Eczema Area and Severity Index from baseline (EASI 90) and a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16 with the treatment of upadacitinib compared with dupilumab in the Intent-to-Treat (ITT) Population. **Primary Endpoint** The primary endpoint is the achievement of a composite endpoint of both EASI 90 and WP-NRS 0/1 at Week 16.

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	Ranked Secondary Endpoints The ranked secondary endpoints are: 1. Achievement of EASI 90 at Week 16. 2. Achievement of WP-NRS 0/1 at Week 16 among subjects with Baseline WP-NRS > 1. 3. Achievement of an improvement (reduction) in WP-NRS ≥ 4 at Week 16 among subjects with Baseline WP-NRS ≥ 4. 4. Achievement of WP-NRS 0/1 at Week 4 among subjects with Baseline WP-NRS > 1. 5. Achievement of WP-NRS 0/1 at Week 2 among subjects with Baseline WP-NRS > 1. 6. Achievement of EASI 90 at Week 4. 7. Achievement of EASI 75 at Week 2. 8. Achievement of EASI 100 at Week 16. **Safety Endpoints** Safety will be assessed by AE monitoring, physical examination, vital signs, and clinical laboratory testing during the study. Laboratory assessments will include hematologic parameters, chemistry, liver function tests, and lipid parameters.
Investigator(s):	Multicenter.
Study Site(s):	Up to 330 sites globally
Study Population and Number of Subjects to be Enrolled:	Approximately 880 adolescent and adult subjects (≥ 12 and < 64 years of age and weighing at least 40 kg) with moderate to severe AD who have inadequate response to systemic therapies.
Investigational Plan:	This is a Phase 3b/4, global, randomized, open-label, efficacy assessor blinded, multi-center study that will evaluate upadacitinib compared with dupilumab, as monotherapy, in adolescents and adult subjects (≥ 12 and < 64 years of age, weighing at least 40 kg) with moderate to severe AD who have inadequate response to systemic therapy. Eligible subjects must have a documented history of inadequate response to at least one systemic treatment for AD prior to the Baseline Visit or for whom other systemic treatments are otherwise medically inadvisable. The study will consist of a 35-day Screening Period; Period 1, a 16-week randomized, open-label, efficacy assessor blinded treatment period for all subjects, and a 30-day or 12-week (84 days) follow-up visit for subjects on upadacitinib or dupilumab respectively, who will not enter Period 2; Period 2, a 16-week open-label, efficacy assessor blinded extension period for those subjects with a < EASI 75 response at Week 16 (total duration 32 weeks) and a 30-day follow-up visit. After the last study visit, a 30-day or 12-week (for subjects receiving upadacitinib or dupilumab, respectively) follow-up visit (or phone call if a visit is not possible) will be completed to determine the status of any new or ongoing AEs/SAEs and concomitant medications. The 30-day or 12-week follow-up phone call (for subjects on upadacitinib or dupilumab, respectively) following the last dose of study drug will not be

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	required for any subject who initiates commercially available upadacitinib or dupilumab upon the study Completion Visit or Premature Discontinuation visit. The study is comprised of two periods: • **Period 1**: A 16-week open-label, efficacy assessor blinded treatment period to evaluate the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose adjusted based on clinical response starting after 4 weeks of treatment, compared with dupilumab as per its label. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive either upadacitinib 15 mg QD or dupilumab as per its label. During Period 1, subjects randomized to upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters is met: • Starting at Week 4, subject has a < EASI 50 response. • Starting at Week 4, subject has a < 4-point improvement from Baseline in WP-NRS (weekly average). • Starting at Week 8, subject has a < EASI 75 response. • **Period 2**: An extension period to evaluate the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose adjusted based on clinical response, in subjects with inadequate response to dupilumab, and treatment at 30 mg QD in subjects with inadequate response to upadacitinib in Period 1. At Week 16 subjects from both treatment arms in Period 1 with a < EASI 75 response will enter Period 2; subjects from the dupilumab arm will be offered the option to receive upadacitinib 15 mg QD while subjects from the upadacitinib arm will either continue (if already receiving 30 mg QD) or be escalated to upadacitinib 30 mg QD (if receiving 15 mg QD) until Week 32. • During Period 2, subjects receiving upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters is met: ○ Starting at Week 20, subject has a < EASI 75 response. ○ Starting at Week 20, subject has a < 4-point improvement from Baseline in WP-NRS (weekly average) **Rescue Therapy** **Period 1** **Upadacitinib arm:** Starting four weeks following dose escalation to upadacitinib 30 mg QD in Period 1, subjects with a < EASI 50 response or < 4-point improvement from Baseline in WP-NRS (weekly average) will have the option to add topical therapy (except for topical JAK inhibitors) as rescue therapy. **Dupilumab arm:** Starting at Week 4 of Period 1 with dupilumab as per its label, subjects with a < EASI 50 response or < 4 point improvement from Baseline in WP-NRS (weekly average), will have the option to add topical therapy (except for topical JAK inhibitors) as rescue therapy.

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	Period 2 Starting four weeks following dose escalation to upadacitinib 30 mg QD in Period 2, subjects with a < EASI 75 response from Baseline or < 4-point improvement from Baseline in WP-NRS (weekly average) will have the option to add topical therapy (except for topical JAK inhibitors) as rescue therapy.
Key Eligibility Criteria:	Key eligibility criteria include: 1. Subjects ≥ 12 years old (≥ 40 kg at Baseline) and < 64 years old at Screening Visit. Subject must not turn 65 years old before completing the study. 2. Chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria. 3. EASI score ≥ 16; vIGA-AD score ≥ 3 and ≥ 10% BSA of AD involvement at the Baseline Visit. 4. Baseline weekly average of daily WP-NRS ≥ 4. 5. Documented history of inadequate response to previous systemic treatment defined as documented history of previous inadequate response to at least one prior systemic treatment for AD OR for whom other systemic treatments are otherwise medically inadvisable.
Study Drug and Duration of Treatment:	In Period 1, subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive either upadacitinib 15 mg QD or dupilumab as per its label. At Week 16 subjects from both treatment arms with a < EASI 75 response will enter Period 2; subjects from the dupilumab arm will be offered the option to receive upadacitinib 15 mg QD while subjects from the upadacitinib arm will either continue (if already receiving 30 mg QD) or be escalated to upadacitinib 30 mg QD (if receiving 15 mg QD) until Week 32.
Date of Protocol Synopsis:	02 May 2023

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2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

The Janus kinase (JAK) or JAKs are a family of intracellular tyrosine kinases that function as dimers in the signaling process of many cytokine receptors.[1] The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases.[2-5] Targeting the JAK signaling pathway for autoimmune diseases is supported by the involvement of various proinflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-related disorders. The activation of JAK signaling initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders.

Upadacitinib is an oral, once-daily, selective, and reversible small-molecule JAK inhibitor, engineered to have greater inhibitory potency for JAK1 versus JAK2, JAK3, and tyrosine kinase 2 (TYK2). Janus kinase 1 inhibition blocks the signaling of many important pro-inflammatory cytokines, including interleukin (IL)-2, IL-6, IL-7, and IL-15, interferon (IFN)-γ, which are known contributors to inflammatory disorders. It also blocks the signaling of IL-4, IL-13, IL-31, IL-22, IFNγ, and thymic stromal lymphopoietin (TSLP) cytokines that play an important role in the pathogenesis of atopic dermatitis (AD). To date, upadacitinib has been approved in at least one country for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), ulcerative colitis (UC), Crohn's disease (CD), and atopic dermatitis (AD). Upadacitinib is also being investigated for patients with giant cell arteritis (GCA), Takayasu arteritis, polyarticular course juvenile idiopathic arthritis (pcJIA), systemic juvenile idiopathic arthritis (sJIA), pediatric AD, pediatric UC, nonsegmental vitiligo, hidradenitis suppurativa (HS), alopecia areata and systemic lupus erythematosus (SLE).

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

In AD, the efficacy and safety of upadacitinib 15 mg and 30 mg once daily (QD) was assessed in three Phase 3 randomized, double-blind, multicenter studies (MEASURE UP 1, MEASURE UP 2 and AD UP),[6-8] and the two doses (upadacitinib 15 mg and 30 mg QD) studied in the pivotal trials for AD were approved for the treatment of moderate to severe AD in several jurisdictions, including but not limited to the European Union (EU), Japan, Canada, and the United States (US), with some differences in the indications or posologies.[9] However, the Phase 3 studies for AD were designed with a stable regimen of upadacitinib 15 mg or 30 mg QD for 5 years and no dose escalation or dose reduction based on the clinical response were assessed.

In addition, the efficacy and safety of upadacitinib 30 mg QD versus dupilumab for the treatment of adult subjects with moderate to severe AD who were candidates for systemic therapy was assessed in a head-to-head, Phase 3b, multicenter, randomized, double-blinded, double-dummy, active-controlled clinical trial (HEADS UP).[10,11] However, the 15 mg QD dose for upadacitinib was not assessed in that trial.

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Dupilumab is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα).

Dupilumab has been approved in at least one country for the treatment of moderate to severe AD, moderate to severe asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis.

In AD, dupilumab has been approved for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy, and for the treatment of severe AD in children 6 to 11 years old who are candidates for systemic therapy in the EU and for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable in the United States (US).[12]

The efficacy and safety of dupilumab as monotherapy and with concomitant topical corticosteroids (TCS) were evaluated in three pivotal randomized, double-blind, placebo-controlled, multicenter studies (SOLO 1, SOLO 2, and CHRONOS)[13,14] in 2,119 patients 18 years of age and older with moderate to severe AD. The efficacy and safety of dupilumab monotherapy in adolescent patients was evaluated in a randomized, double-blind, placebo-controlled, multicenter study (AD-1526)[15] in 251 adolescent patients 12 to 17 years of age with moderate-to-severe AD.

This study aims to provide data on the efficacy and safety of upadacitinib initiated at 15 mg QD and dose escalated based on the clinical response, compared with dupilumab as per its label, after 16 weeks of treatment.

Additionally, this study aims to provide data on the efficacy and safety of upadacitinib initiated at 15 mg QD and dose adjusted based on clinical response in subjects with inadequate response to dupilumab.

Clinical Hypothesis

The primary hypothesis is that upadacitinib, initiated at 15 mg QD and dose escalated based on clinical response will demonstrate superior efficacy compared to dupilumab and will be well tolerated in adult and adolescent subjects with moderate to severe AD who have inadequate response to a systemic therapy.

2.2 Benefits and Risks to Subjects

In the EU SmPC, upadacitinib has been approved for the treatment of moderate to severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy.[9]

The recommended dose is upadacitinib 15 mg or 30 mg QD based on individual patient presentation. A dose of 15 mg QD is recommended for patients with risk factors for venous thromboembolism, major adverse cardiovascular events (MACE), and malignancy. A dose of 30 mg QD may be appropriate for patients with high disease burden who have no known risk factors for venous thromboembolism, MACE, and malignancy, or for patients with an inadequate response to 15 mg QD. The lowest effective dose for maintenance should be used.[9]

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For patients ≥ 65 years of age the recommended dose is upadacitinib 15 mg QD.[9] The recommended dose of upadacitinib for adolescents (from 12 to 17 years of age) weighing at least 30 kg is upadacitinib 15 mg QD.[9] The above indication and posology correspond to the European Union and may vary within different jurisdictions.

In the US USPI, upadacitinib has been approved for adults and pediatric patients 12 years of age and older with refractory, moderate to severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when the use of those therapies are inadvisable. Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

The recommended dosage for pediatric patients 12 years of age and older weighing at least 40 kg and adults less than 65 years of age is to initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue upadacitinib if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.

The efficacy and safety of upadacitinib 15 mg and 30 mg QD was assessed in 3 Phase 3 randomized, double-blind, multicenter studies (MEASURE UP 1, MEASURE UP 2, and AD UP) in a total of 2584 subjects (12 years of age and older).[6-8] A significantly greater proportion of subjects treated with upadacitinib 15 mg or 30 mg QD achieved validated Investigator´s Global Assessment for AD (vIGA-AD) 0 or 1, Eczema Area and Severity Index (EASI) 75, EASI 90, EASI 100, Dermatology Life Quality Index (DLQI) 0 or 1, or a ≥ 4-point improvement on the Worst Pruritus Numerical Rating Scale (WP-NRS) compared to placebo at Week 16. Rapid improvements in skin clearance and itch were also achieved. Results at Week 16 were maintained through Week 52 in subjects treated with upadacitinib 15 mg or 30 mg QD.

Adverse events (AEs) such as infections including herpes zoster reactivation, major adverse cardiovascular events (MACE defined as cardiovascular death, non-fatal myocardial infarctions, and non-fatal strokes), thrombosis, malignancies, hypersensitivity (serious anaphylactic reaction and angioedema), gastrointestinal perforation, bone fracture, and some laboratory abnormalities have been observed in patients receiving JAK inhibitors including upadacitinib.

An increased risk of infections including opportunistic infections (e.g., mucosal candida infections) and herpes zoster, non-melanoma skin cancer (NMSC), and abnormal laboratory changes (e.g., elevations of serum transaminases, lipids, creatine phosphokinase [CPK], and reductions in hemoglobin and white blood cells [WBC]) have been observed with upadacitinib therapy.

In ORAL Surveillance, a study of a different JAK inhibitor, tofacitinib, in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of all-cause mortality, malignancies, MACE and thrombosis (overall thrombosis, deep vein thrombosis, and pulmonary embolism) were seen in patients treated with tofacitinib versus TNF blockers.[7,16] These higher rates were primarily observed in patients 65 years of age and older, patients with a history of atherosclerotic cardiovascular disease, and current or past long-time smokers. Although upadacitinib clinical trial data to date have not indicated a higher risk for MACE, venous thromboembolism, malignancies excluding NMSC, or deaths in RA patients treated with upadacitinib versus adalimumab, the findings of the ORAL Surveillance study may also apply to other JAK inhibitors and an increased risk for these events compared to TNF blockers cannot be completely excluded. Therefore, the investigator should consider the benefits and risks of upadacitinib treatment and suitable treatment alternatives in determining study participation and the continued use

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of upadacitinib in patients 65 years of age and older, patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, patients who are current or past long-time smokers, and/or patients with other malignancy risk factors (e.g., current malignancy or history of malignancy).

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

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

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

Dupilumab has been approved for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy, and for the treatment of severe AD in children 6 to 11 years old who are candidates for systemic therapy in the EU[17] and for the treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable in the United States (US).[12]

Although dupilumab addresses the needs of some patients with moderate to severe AD, a large unmet need still exists in this population since, in the dupilumab Phase 3 studies (even when combined with topical corticosteroids [TCS]), fewer than 40% of the adult patients achieved 0 or 1 on the Investigator's Global Assessment (IGA) scale.[13,14] This percentage was lower for adolescents, as 24.4 % of subjects included in the study achieved a 0 or 1 on the IGA at Week 16.

Therefore, a large proportion of patients continued to experience significant symptoms on dupilumab therapy. Nearly 50% of dupilumab adult subjects who were IGA 0 or 1 responders at Week 16 became nonresponders by Week 52.[17] Dupilumab is generally well-tolerated, and the most common adverse events (AEs) are injection site reaction, conjunctivitis, and blepharitis.

Considering the coronavirus – 2019 (COVID-19) pandemic and based on the information to date, it is unknown whether study participants treated with upadacitinib may be at an increased risk for COVID-19 or experience more serious illness if infected. The data thus far do not show that patients on upadacitinib treatment have worse outcomes of COVID.

For further details, please see findings from completed studies, including safety data in the current upadacitinib Investigator's Brochure.[18,19]

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3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Objectives

Primary

The primary study objective, related to Study Period 1, is to assess the efficacy and safety of upadacitinib, initiated at 15 mg once daily (QD) and dose adjusted based on clinical response, compared with dupilumab as per its label.

An additional objective, related to Study Period 2, is to assess the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose adjusted based on clinical response, in subjects with inadequate response to dupilumab.

The primary efficacy objective is based on the achievement of a composite endpoint of at least a 90% reduction in EASI from baseline (EASI 90) and a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16 with the treatment of upadacitinib compared with dupilumab per its label in the Intent-to-Treat (ITT) Population, which consists of all randomized subjects (Section 7.2).

Secondary

The secondary efficacy objectives are based on ranked secondary endpoints as defined in Section 3.3 with the treatment of upadacitinib compared with dupilumab in the ITT Population.

Hypotheses and Estimands for the Primary and Ranked Secondary Endpoints

The hypothesis corresponding to the primary efficacy endpoint (Section 3.2) is:

- The proportion of subjects achieving both EASI 90 and WP-NRS 0/1 at Week 16 in those treated with upadacitinib is greater than those treated with dupilumab.

The estimand corresponding to the primary endpoint is defined using the composite variable strategy, as follows:

- Difference in the proportion of subjects achieving both EASI 90 and WP-NRS 0/1 at Week 16 without the use of rescue medication, regardless of treatment discontinuation, between upadacitinib and dupilumab in the adolescent and adult subjects with moderate to severe AD who have inadequate response to systemic therapy.

The hypotheses and estimands corresponding to the ranked secondary endpoints are summarized below.

- Hypotheses: the proportion of subjects achieving each ranked endpoint in those treated with upadacitinib is greater than those treated with dupilumab

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- Estimands: Difference in proportion of subjects achieving each of ranked secondary endpoints without the use of rescue medication, regardless of treatment discontinuation, between upadacitinib and dupilumab in the adolescent and adult subjects with moderate to severe AD who have inadequate response to systemic therapy.

3.2 Primary Endpoint

The primary endpoint is the achievement of a composite endpoint of both EASI 90 and WP-NRS 0/1 at Week 16.

3.3 Secondary Endpoints

Ranked Secondary Endpoints

1. Achievement of EASI 90 at Week 16.
2. Achievement of WP-NRS 0/1 at Week 16 among subjects with Baseline WP-NRS > 1.
3. Achievement of an improvement (reduction) in WP-NRS ≥ 4 at Week 16 among subjects with Baseline WP-NRS ≥ 4.
4. Achievement of WP-NRS 0/1 at Week 4 among subjects with Baseline WP-NRS > 1.
5. Achievement of WP-NRS 0/1 at Week 2 among subjects with Baseline WP-NRS > 1.
6. Achievement of EASI 90 at Week 4.
7. Achievement of EASI 75 at Week 2.
8. Achievement of EASI 100 at Week 16.

3.4 Additional Efficacy Endpoints

In addition to Week 16 assessments, the primary and ranked secondary efficacy endpoints will be evaluated at all scheduled visits in Period 1 and Period 2 as noted in the Study Activities Table (Appendix D) during which the assessments are measured.

The following endpoints will also be evaluated at all scheduled visits in Period 1 and Period 2 during which the assessments are measured as noted in the Study Activities Table (Appendix D):

- Achievement of EASI 75/90/100 at Week 32 for subjects who received dupilumab/upadacitinib in Period 1 and did not achieve EASI 75 at Week 16.
- Achievement of EASI 90 AND WP-NRS 0/1 at Week 32 for subjects who received dupilumab/upadacitinib in Period 1 and did not achieve EASI 90 AND WP-NRS 0/1 at Week 16.
- Achievement of an improvement (reduction) in WP-NRS ≥ 4 at Week 32 for subjects who had WP-NRS ≥ 4 at Baseline and who received dupilumab/upadacitinib in Period 1 and did not achieve WP-NRS reduction ≥ 4 at Week 16.

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- Achievement of WP-NRS 0/1 at Week 32 for subjects who had WP-NRS > 1 at Baseline and who received dupilumab/upadacitinib in Period 1 and did not achieve WP-NRS 0/1 at Week 16.
- Achievement of 75% reduction in EASI in each body region from Baseline;
- Achievement of 75% reduction in EASI in the head and neck body region at Week 32 for subjects who received dupilumab/upadacitinib in Period 1 and did not achieve 75% reduction in EASI in the head and neck body region at Week 16.

3.5 Safety Endpoints

Safety will be assessed by AE monitoring, physical examination, vital signs, imaging, and clinical laboratory testing during the study. Laboratory assessments will include hematologic parameters, chemistry, liver function tests, and lipid parameters. Tanner Stage assessments will be included for adolescent subjects.

3.6 Biomarker Research Endpoints

Optional biospecimens (e.g., skin biopsies, whole blood for plasma, serum, and DNA) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease related or drug related biomarkers in circulation. Types of biomarkers may include nucleic acids, proteins, lipids, cellular populations, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to: serum and plasma proteomic and genomic evaluations, transcriptomic, genetic, and histologic analysis to evaluate biomarker endpoints related to safety, disease state, response to treatment, and target pathway. The biomarker research results may not be included with the clinical study report. Further details regarding the biomarker research and collection time points are located in the Operations Manual Section 2.1, and Section 3.7.

Optional biospecimens will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples as described.

No biomarker samples will be collected in China.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a global, Phase 3b/4, randomized, open-label, efficacy assessor-blinded, multicenter study that will evaluate upadacitinib compared with dupilumab per its label, as monotherapy, in adolescents and adult subjects (≥ 12 and < 64 years of age weighing at least 40 kg) with moderate to severe AD who have inadequate response to systemic therapy. Eligible subjects must have a documented history of inadequate response to at least one systemic treatment for AD prior to the Baseline Visit or for whom other systemic treatments are otherwise medically inadvisable.

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The study will consist of a 35-day Screening Period; Period 1, a 16-week randomized, open-label, efficacy assessor blinded treatment period for all subjects, and a 30-day or 12-week follow-up visit for subjects on upadacitinib or dupilumab respectively, who will not enter the Period 2; Period 2, a 16-week open-label, efficacy assessor blinded extension period for those subjects with a < EASI 75 response at Week 16 (total duration 32 weeks) and a 30-day follow-up visit.

The study is comprised of two periods:

- **Period 1**: A 16-week open-label, efficacy assessor blinded treatment period designed to evaluate the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose adjusted based on clinical response starting after 4 weeks of treatment, compared with dupilumab as per its label. Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to receive either upadacitinib 15 mg QD or dupilumab as per its label.
- **Period 2**: An open-label, efficacy assessor blinded extension period to evaluate the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose adjusted based on clinical response in subjects with inadequate response to dupilumab, and treatment at 30 mg QD in subjects with inadequate response to upadacitinib in Period 1. At Week 16, subjects from both treatment arms with a < EASI 75 response will enter Period 2; subjects from the dupilumab arm will be offered the option to receive upadacitinib 15 mg QD while subjects from the upadacitinib arm will either continue (if already receiving 30 mg) or be escalated to upadacitinib 30 mg QD (if receiving 15 mg QD) until Week 32.

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

- **Upadacitinib arm** (N = 440): Daily oral doses of upadacitinib 15 mg QD from the Baseline visit until the Week 16 visit. During Period 1, subjects randomized to upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters is met:
  - Starting at Week 4, subject has a < EASI 50 response
  - Starting at Week 4, subject has a < 4-point improvement from Baseline in WP-NRS (weekly average)
  - Starting at Week 8, subject has a < EASI 75 response

  At Week 16, subjects receiving upadacitinib 15 mg QD or 30 mg QD, will be reassigned based on their EASI response:

  - < EASI 75 will be allocated or continue to receive oral doses of upadacitinib 30 mg QD in Period 2
  - ≥ EASI 75 will complete end of study procedures.
- **Dupilumab arm** (N = 440):
- Adults: Dupilumab 600 mg (2 × 300 mg dupilumab SC injection) administered at the Baseline visit, followed by dupilumab 300 mg SC injection EOW until the Week 16 visit.
- Adolescents: Adolescents (12 to 17 years of age and weighing at least 40 kg).

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Dose of dupilumab for subcutaneous administration in adolescent patients 12 to 17 years of age with AD.

Body weight of subject at Screening Visit and at each visit:

1. 40 to < 60 kg:
    - Initial dose: 400 mg (two 200 mg injections)
    - Subsequent doses (EOW): 200 mg
2. 60 kg or more:
    - Initial dose: 600 mg (two 300 mg injections)
    - Subsequent doses (EOW): 300 mg

- At Week 16, subjects receiving dupilumab as per its label will be reassigned based on their EASI response:
    - < EASI 75 will be offered the option to receive oral doses of upadacitinib 15 mg QD and enter Period 2
    - ≥ EASI 75 will complete end of study procedures
- During Period 2, subjects randomized to upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters is met:
    - Starting at Week 20, subject has a < EASI 75 response
    - Starting at Week 20, subject has a < 4-point improvement from Baseline in WP-NRS (weekly average)

An unscheduled visit may be used for this purpose if necessary for dose escalation.

Any subject treated for at least 8 weeks with upadacitinib 30 mg QD with a < EASI 50 response (reduction from Baseline) after rescue with topical corticosteroid treatment for at least 1 week must be discontinued.

Randomization will be stratified by baseline disease severity (moderate validated Investigator Global Assessment for AD [vIGA-AD 3] vs. severe [vIGA-AD 4]) and age categories (12 to < 18; 18 to < 40; ≥ 40 to < 64 years).

During Period 1 and Period 2 which are open-label, only the efficacy assessor will be blinded to the subject's treatment assignment. Subjects and other study site personnel will be aware of the subject's treatment assignment.

Further details regarding study procedures are located in the Operations Manual. See Section 5 for information regarding eligibility criteria.

The primary analysis for the study will be performed when all ongoing subjects have completed Week 16 or permanently discontinue Period 1. This analysis is the final and only analysis for the primary and ranked secondary endpoints. Additional analyses may be performed as appropriate.

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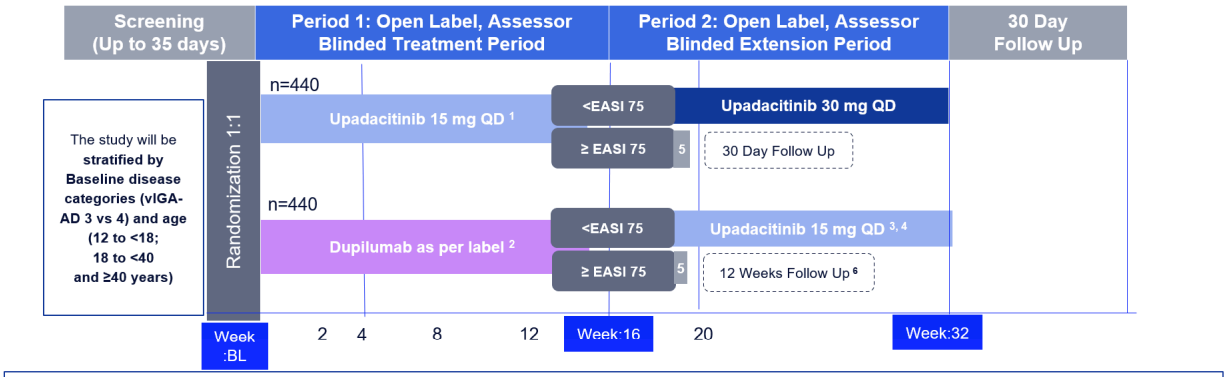
Figure 1. Study Schematic



[1] **Upadacitinib treatment Strategy:**
During Period 1, subjects randomized to upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters is met:
- Starting at Week 4, subject has a <EASI50 response
- Starting at Week 4, subject has a <4-point improvement in Worst Pruritus NRS
- Starting at Week 8, subject has a <EASI 75 response

[2] **Dupilumab dosing as per label**
- Adults: Dupilumab 600 mg (2 × 300 mg dupilumab SC injection) at Baseline , followed by dupilumab 300 mg SC injection EOW until the Week 16
- Adolescents: 12 to 17 years and ≥ 40 kg
  1. 40 to < 60 kg: Initial dose: Dupilumab 400 mg (two 200 mg injections); Subsequent doses (every other week): 200 mg
  2. ≥ 60 kg: Initial dose: Dupilumab 600 mg (two 300 mg injections); Subsequent doses (every other week): 300 mg

[3] **Subjects randomized to dupilumab as per label in Period 1 and having <EASI 75 response at Week 16 will be offered the option to enter Period 2 and receive upadacitinib 15 mg QD.**
[4] **During Period 2, subjects reassigned to receive upadacitinib 15 mg QD will have their dose increased to 30 mg QD if any of the following parameters is met:**
- Starting at Week 20 subject has a <EASI75 response
- Starting at Week 20, subject has a <4-point improvement in Worst Pruritus NRS

[5] **Subjects will discontinue the Study**
[6] **The 12 week follow up includes the 2 weeks after last dose of dupilumab plus 10 weeks after the Week 16 visit.**

BL = Baseline; EOW = every other week; EASI 50/75 = Eczema Area and Severity Index 50/75; QD = once daily; SC= subcutaneous; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis

4.2 Discussion of Study Design

Choice of Control Group

Dupilumab is a systemic therapy approved in the US, EU, and elsewhere for treatment of adult and adolescent patients with moderate to severe AD. One upadacitinib Phase 3b study (HEADS UP)[10,11] in a similar patient population showed superior results for upadacitinib 30 mg QD versus dupilumab 300 mg every other week (EOW) at Week 16. This study is being performed to evaluate the hypothesis of potential superiority of upadacitinib, initiated at 15 mg QD and dose escalated based on clinical response versus dupilumab as per its label.

Appropriateness of Measurements

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

Care should be taken to minimize the pain and discomfort of laboratory procedures. Use of a butterfly needle for venipuncture and/or a needle gauge appropriate for vein size may optimize the comfort for some individuals. Attempts at venipuncture should be limited to the subject's tolerance of the

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procedure; after more than 2 unsuccessful attempts for venipuncture, consider requesting the subject to return at a later time for the blood sample collection within the timeframe allowed by the protocol.

Suitability of Subject Population

The target study population for this study represents an adolescent and adult AD population with moderate to severe disease activity with documented history of inadequate response to at least one prior systemic treatment for AD. Adolescent and adult subjects ≥ 12 and < 64 years of age and weighing at least 40 kg will be eligible for the study.

Selection of Doses in the Study

This study will evaluate two doses of upadacitinib (15 mg and 30 mg QD).

This study is also assessing 2 doses of dupilumab, which will be used according to its current label dosage for both adults and adolescents (≥ 40 kg).

All subjects in the upadacitinib arm will receive 15 mg QD as the starting dose. The dose will be adjusted based on clinical response starting after 4 weeks of treatment when needed and according with the protocol criteria.

The dose selection was informed by the two doses studied in the pivotal trials to support the approvals of market authorizations of moderate to severe AD in several jurisdictions, including but not limited to the EU, Japan, US, and Canada. Both doses showed a positive benefit-risk and the objective of this study is to generate data that will help inform the use of both approved doses.

All the current available pharmacokinetic (PK), pharmacodynamic, safety, and efficacy data from upadacitinib studies were used to support the selection of these doses.

Exposures associated with upadacitinib 30 mg or 15 mg QD using the once daily formulation are predicted to be efficacious in treatment of subjects with moderate to severe AD with limited effects on laboratory parameters.

The selection of the dupilumab doses was based on the approved posology in moderate to severe AD subjects, initial dose of 600 mg (two 300 mg injections), followed by 300 mg given EOW administered as subcutaneous injection for adults, initial dose of 400 mg (two 200 mg injections), followed by 200 mg EOW administered as subcutaneously (SC) injection for adolescents 12 to 17 years of age weighing between 30 kg and less than 60 kg, and initial dose of 600 mg (two 300 mg injections), followed by 300 mg given EOW administered as subcutaneous injection for adolescents 12 to 17 years of age weighing 60 kg or more.[17,20]

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study, in consideration of the benefits and risks of treatment with upadacitinib (Section 2.2):

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Consent

- 1. Adult subjects ≥ 18 years of age at Screening Visit or their legally authorized representative must voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures and comply with the requirements of this study protocol.
- 2. For subjects ≥ 12 and < 18 years of age at Screening Visit: Parent or legal guardian, as required, has voluntarily signed and dated an informed consent form, approved by an IEC, after the nature of the study has been explained and the subject's parent or legal guardian has had the opportunity to ask questions. Subjects will be included in all discussions in order to obtain verbal/and or written assent. Parent/legal guardian and subject must comply with the requirements of this study protocol. If a subject becomes of legal age during the course of the study, that subject will need to be consented using the approved informed consent form.

Demographics and Laboratory Assessments

- 3. Subjects must be at least ≥ 12 years old and < 64 years old at Screening Visit. Adolescent subjects (between ≥ 12 and < 18 years of age and weighing ≥ 40 kg) may be enrolled only if there is local approval for dupilumab in this age group. Subject must not turn 65 years old before completing the study.
- 4. Body weight must be ≥ 40 kg at the Baseline Visit for subjects between ≥ 12 and < 18 years of age, unless there are higher weight requirements per the local approved label for dupilumab, in which case the more restricted requirement must be followed.
- 5. **Laboratory values** meeting the following criteria within the Screening Period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) ≤ 2× upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) ≤ 2× ULN;
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula ≥ 40 mL/min/1.73 m^2 for adult subjects and adolescent subjects (12 - 17 years of age);
  - Total white blood cell (WBC) count ≥ 2,500/µL;
  - Absolute neutrophil count (ANC) ≥ 1,200/µL;
  - Platelet count ≥ 100,000/µL;
  - Absolute lymphocyte count (ALC) ≥ 750/µL;
  - Hemoglobin ≥ 9 g/dL.

AD Disease history

- 6. Chronic AD with onset of symptoms at least 3 years prior to baseline and subject meets Hanifin and Rajka criteria.[21]
- 7. Subject meets the following disease activity criteria:

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- EASI score ≥ 16; vIGA-AD score ≥ 3 and ≥ 10% BSA of AD involvement at theBaseline Visit;
- Baseline weekly average of daily WP-NRS ≥ 4. Note: The baseline weekly average of daily WP-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.
- Documented history of inadequate response to previous systemic treatment defined as documented history of previous inadequate response to at least one prior systemic treatment for AD OR for whom other systemic treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
- Subject has applied a topical emollient (an additive-free, bland emollient moisturizer) twice daily for at least 7 days before the Baseline Visit and for the duration of the study. Note: Subject may use prescription moisturizers or moisturizers containing ceramide, urea, filaggrin degradation products or hyaluronic acid if such moisturizers were initiated before the Screening visit.

Subject History

- 8. Subject is judged to be in good health as determined by the Principal Investigator, based upon the results of the Screening assessments and medical history.
- 9. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.
- 10. Subject must have no current or past history of infection including:
  - Other active skin diseases or skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline Visit or would interfere with the appropriate assessment of AD lesions;
  - Two or more episodes of herpes zoster, or one or more episodes of disseminated herpes zoster;
  - One or more episodes of disseminated herpes simplex (including eczema herpeticum);
  - Human immunodeficiency virus (HIV) infection defined as confirmed positive anti-HIV antibody (HIV Ab) test;
  - Active tuberculosis (TB) or meet TB exclusionary parameters (specific requirements for TB testing are provided in the Operations Manual);
  - Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the Baseline Visit;
  - Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
  - COVID-19 infection: In subjects who tested positive for COVID-19, at least 5 days must have passed since a COVID-19 positive test result for study entry of asymptomatic subjects. Subjects with mild/moderate COVID-19 infection can be enrolled if fever is resolved without use of antipyretics for 24 hours and other symptoms improved, or if 5 days have passed

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since the COVID-19 positive test result (whichever comes last). Subjects may be rescreened if deemed appropriate by the investigator based upon the subject's health status.

- Subjects must not have evidence of:
- HBV: hepatitis B surface antigen (hepatitis B [HB] Ag) positive (+) test or detectable hepatitis B virus (HBV) deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for Hepatitis B surface antibody positive [+] subjects where mandated by local requirements);
- HCV: detectable HCV ribonucleic acid (RNA) in any subject with anti-HCV antibody (HCV Ab).
- **For Japan:** Positive result of beta-D-glucan (screening for *Pneumocystis jirovecii* infection) or two consecutive indeterminate results of beta-D-glucan during the Screening Period.

✔ 11. Subject must not have any of the following medical diseases or disorders:

- Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting, and aorto-coronary bypass surgery;
- Any other unstable clinical condition which, in the opinion of the investigator, would put the subject at risk by participating in the protocol;
- Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization;
- History of an organ transplant which requires continued immunosuppression;
- Subject must not have a 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;
- History of gastrointestinal (GI) perforation (other than due to appendicitis or mechanical injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment;
- Conditions that could interfere with drug absorption including but not limited to short bowel syndrome or gastric bypass surgery; subjects with a history of gastric banding/segmentation are not excluded;
- History of malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.

✔ 12. No reason the investigator believes that the subject is an unsuitable candidate to participate in the study, receive study drug, or would be placed at risk by participating in the study.

✔ 13. For France, subjects must be registered with a social security scheme. Subjects may not fall within the scope of Article L1121-6 of the French Public Health Code (persons deprived of their freedom further to a judicial or administrative decision, persons receiving psychiatric care and persons admitted to a health and social facility for reasons unrelated to the study) or Article L1121-8 (adults under a legal protection order or unable to express their consent).

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Contraception

- 14. A negative serum pregnancy test for all female subjects considered to be of childbearing potential (as defined in Section 5.2) at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 15. If female of childbearing potential (as defined in Section 5.2), must be practicing at least 1 protocol-specified method of birth control, that is effective from Study Day 1 (or earlier) through at least 30 days or 12 weeks after the last dose of study drug (for upadacitinib or dupilumab, respectively).
- 16. For all females of child-bearing potential (as defined in Section 5.2): must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at Baseline prior to the first dose of study drug (local practices may require serum pregnancy testing at Baseline). Subjects with a borderline serum pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological causes of borderline results and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements). Subjects with a urine pregnancy test at Baseline that is borderline or ambiguous must have a serum pregnancy test. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- 17. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from Study Day 1 through at least 30 days after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential do not need to use birth control.
- 18. Female subjects must not be pregnant, breastfeeding, or considering becoming pregnant during the study and through at least 30 days or 12 weeks after the last dose of study drug (for upadacitinib or dupilumab, respectively).

Prior and Concomitant Medications

- 19. No prior exposure to any oral or topical JAK inhibitor (including but not limited to upadacitinib [Rinvoq®], tofacitinib [Xeljanz®], ruxolitinib [Jakafi® or Opzelura®], baricitinib [Olumiant®], peficitinib [Smyraf®], abrocitinib [Cibinqo®], filgotinib [Jyseleca®], fedratinib [Inrebic®], and deucravacitinib [Sotyktu™]).
- 20. No prior exposure to dupilumab, tralokinumab, or lebrikizumab.
- 21. Subjects must not have used the following AD treatments within the specified time frame prior to Baseline Visit:
  - Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-γ and mycophenolate mofetil within 4 weeks;
  - Topical treatments including but not limited to TCS, TCIs, or topical PDE-4inhibitors within 7 days.
  - Targeted biologic treatments within 5 half-lives [if known] or within 12 weeks, whichever is longer

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- Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks;
- Oral or parenteral traditional Chinese medicine within 4 weeks.

✔ 22. Subject must not have been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study.

✔ 23. Subject must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from Screening through the end of study drug administration or strong CYP3A inducers 30 days prior to baseline through the end of study drug administration (refer to Table 1 for examples of commonly used strong CYP3A inhibitors and inducers). Subjects may not use herbal therapies or other traditional medicines with unknown effects on CYP3A from baseline through the end of study drug administration.

✔ 24. Subject must not have received any live vaccine with replicating potential within 30 days (or longer if required locally) prior to the first dose of study drug, or have expected need of vaccination with any live vaccine with replicating potential during study participation including at least 30 days or 12 weeks (or longer if required locally) after the last dose of study drug (for upadacitinib or dupilumab, respectively). Live vaccines that are incapable of replicating are permitted.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

Females, Non-Childbearing Potential

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

1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
   - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
   - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
2. Postmenopausal female:
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.
3. Premenarchal female (have not met the definition of childbearing potential below).

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- Females who are Tanner Stage 1 or 2 who have not experienced menarche (at least one menstrual period). Tanner Stage must be established and documented through investigator-or delegated, trained medical professional assessment.

- Females of Childbearing Potential

  Females who have experienced menarche, or who are Tanner Stage 3 or higher who have not experienced menarche will be considered to be of childbearing potential. Tanner Stage must be established and documented through investigator-or delegated, trained medical professional assessment.

  Females that are not postmenopausal and not premenopausal with permanent sterility or permanent infertility (as per the definition of a female of non-childbearing potential above) are considered females of childbearing potential.

  Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days or 12 weeks after the last dose of study drug (for upadacitinib or dupilumab, respectively). Females must commit to use a highly effective method of contraception listed below (failure rate of <1% per year, when used consistently and correctly) plus a barrier method, if indicated below or required per local practice:

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

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

Contraceptive counseling

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

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Females for whom the childbearing potential changes during the study due to meeting any of the criteria for non-childbearing potential above do not need to continue using birth control during or following study drug treatment.

FOR ADOLESCENTS (≥ 12 YEARS TO <18 YEARS OF AGE)

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

Females, Non-Childbearing Potential

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

1. Premenarchal female who has not met the definition of childbearing potential below
    - Females who are Tanner Stage 1 or 2 who have not experienced menarche (at least one menstrual period). Tanner Stage must be established and documented through investigator-or delegated, trained medical professional assessment.
2. Female with permanent infertility due to one of the following:
    - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

Females, of Childbearing Potential

- Females who have experienced menarche, or who are Tanner Stage 3 or higher who have not experienced menarche will be considered to be of childbearing potential. Tanner Stage must be established by an investigator-or delegated, trained medical professional assessment.
- Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days or 12 weeks after the last dose of study drug (for upadacitinib or dupilumab, respectively).
- Females must commit to use a highly effective method of contraception listed below (failure rate of <1% per year, when used consistently and correctly) plus a barrier method, if indicated below:
    - Practice true abstinence (unless not acceptable per local practices), defined as: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
    - Oral, intravaginal, and transdermal combined (estrogen and progestogen-containing) OR oral or injectable progestogen-only hormonal birth control associated with inhibition of ovulation initiated at least 30 days prior to study Baseline
        - PLUS a barrier method (preferably a male condom with or without spermicide; other barrier options are female condom, cap, diaphragm, or sponge with spermicide).
    - Implantable progestogen-only hormonal birth control associated with inhibition of ovulation initiated at least 30 days prior to study Baseline

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- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).

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

Change in Female Subject's Childbearing Potential or Pregnancy Risk During the Study

If the subject's childbearing potential changes after start of the study (e.g., a premenarchal female participant reaches Tanner 3 and/or menarche), or the risk of pregnancy changes (e.g., a female who is not heterosexually active becomes active), the participant and/or their legally authorized representative must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered. The discussion should be documented in the subject's source records.

Contraceptive counseling

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

5.3 Prohibited Medications and Therapy

Biologic Therapies

Current and concomitant biologic therapies and biosimilar versions of biologic drugs that are considered immune modulating (or immune suppressing) are prohibited during treatment with the study drug.

Subjects must have discontinued biologic therapies with immunosuppressive potential prior to the first dose of study drug as specified in the washout procedures (Eligibility Criterion 20, Protocol Section 5.1), OR at least five times the mean terminal elimination half-life of the medication prior to the first dose of study drug. No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented.

Biologic therapies with immunosuppressive potential are prohibited through the end of study drug administration, and include, but are not limited to, the following:

- Abatacept
- Adalimumab
- Anakinra
- Anifrolumab
- Belimumab
- Certolizumab
- Dupilumab
- Etanercept

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- Golimumab
- Guselkumab
- Infliximab
- Ixekizumab
- Lebrikizumab
- Natalizumab
- Nemolizumab
- Risankizumab
- Rituximab
- Secukinumab
- Tocilizumab
- Tralokinumab
- Ustekinumab
- Vedolizumab

Other Non-Biologic Systemic Therapy

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

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

Oral antihistamines are allowed per investigator discretion for the duration of the study.

See also Section 5.4 for further details on allowed rescue.

Corticosteroids

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

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

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Strong CYP3A Inhibitors or Inducers (includes over-the-counter or prescription medicines, vitamins and/or herbal supplements).

Systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors is not permitted from Screening through the end of study drug administration. Use of strong CYP3A inducers is not permitted from 30 days prior to study drug administration through the end of study drug administration. Table 1 includes examples of commonly used strong CYP3A inhibitors and inducers. In addition, herbal therapies and other traditional medicines with unknown effects on CYP3A are not permitted from Screening through the end of study drug administration.

Table 1. Examples of Commonly Used Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir Ceritinib Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Idelalisib Itraconazole Ketoconazole Mibefradi Nefazodone Nelfinavir Posaconazole Ritonavir (alone or in combination with danoprevir, elvitegravir, indinavir, lopinavir, nirmatrelvir, paritaprevir, saquinavir, telaprevir, tipranavir, ombitasvir, and/or dasabuvir) Telithromycin Troleandomycin Voriconazole	Apalutamide Carbamazepine Enzalutamide Ivosidenib Lumacaftor Mitotane Phenytoin Rifampin (Rifampicin) Rifapentine St. John's Wort

Investigational Drugs

Subjects who have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in this study. Investigational drugs are also prohibited during treatment with study drug.

Phototherapy, Tanning Booth, and Extended Sun Exposure

Ultra-violet (UV) B or UVA phototherapy including psoralen and ultraviolet A (PUVA), or laser therapy are not allowed during the study. Tanning booth use or extended sun exposure that could affect disease severity or interfere with disease assessments are not allowed during treatment with study drug.

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Topical Therapy

No topical treatments for AD should be started for the duration of the treatment with study drug except for rescue treatment (see Rescue Concomitant Medications and Therapy, Section 5.4). This includes but is not limited to calcineurin inhibitors, corticosteroids, and phosphodiesterase-4 inhibitors. Prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin are prohibited unless initiated prior to Screening. Additive-free, bland topical emollient treatments are allowed per Eligibility Criteria.

Topical anti-infectives, topical antihistamines, and bleach baths are allowed per investigator discretion for the duration of the study.

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

Other Medications Prohibited during the Study

Oral and topical JAK inhibitors (e.g., commercial upadacitinib [Rinvoq®], tofacitinib [Xeljanz®], ruxolitinib [Jakafi® or Opzelura®], baricitinib [Olumiant®], peficitinib [Smyraf®], abrocitinib [Cibinqo®], filgotinib [Jyseleca®], fedratinib [Inrebic ®], and deucravacitinib [Sotyktu™]).

Treatment with a live (attenuated) vaccine with replicating potential.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of screening, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF). Also, medications taken for AD since date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, route of administration.

For sites in China only, subjects must record concomitant medication on the subject paper diary cards (see Section 5.11).

Vaccines

If the subject and investigator choose to receive/administer live vaccines with replicating potential, these vaccinations must be completed (per local label) at least 30 days (or longer if required locally) before first dose of study drug. Live vaccines with replicating potential are prohibited during study participation including at least 30 days or 12 weeks for upadacitinib or dupilumab, respectively (or longer if required locally) after the last dose of study drug. If a subject requires to receive a live vaccine with replicating potential, this subject should permanently discontinue the study participation prior to receiving the live vaccine. Varicella (chicken pox) vaccination status will be recorded as part of a subject's medical history. Examples of live vaccines with replicating potential include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);

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- Seasonal trivalent live influenza (intranasal);
- Herpes zoster (Zostavax®, live attenuated);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles-mumps-rubella-varicella;
- Oral polio vaccine;
- Smallpox or monkeypox vaccine capable of replicating (ACAM2000®);
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid (oral).

If the live herpes zoster vaccine is to be administered (at least 30 days [or longer if required locally] before first dose of study drug), and there is no known history of primary varicella infection (chicken pox), preexisting immunity to varicella should be confirmed with antibody testing at or prior to Screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative, the live herpes zoster vaccine should not be administered.

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

Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid or biosynthetic include, but are not limited to, injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted), pertussis (Tdap) vaccines and SARS-CoV-2 (inactivated, mRNA, RNA) vaccines. Whenever possible, subjects should not have received a COVID-19 vaccination in the 7 days prior to randomization or plan to receive a COVID-19 vaccination within the first 7 days after initiation of study drug. Viral vector vaccines that are not of replicating potential (such as Convidecia and Convidecia Air to treat Covid-19) are allowed.

Rescue Concomitant Medications and Therapy

Period 1

Upadacitinib arm: Starting four weeks following dose escalation to upadacitinib 30 mg QD in Period 1, subjects with a < EASI 50 response or < 4-point improvement from Baseline in WP-NRS (weekly average) will have the option to add topical therapy (except for topical JAK inhibitors) as rescue therapy.

Dupilumab arm: Starting at Week 4 of Period 1 with dupilumab as per its label, subjects with a < EASI 50 response or < 4-point improvement from Baseline in WP-NRS (weekly average), will have the option to add topical therapy (except for topical JAK inhibitors) as rescue therapy.

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Period 2

Starting four weeks following dose escalation to upadacitinib 30 mg QD in Period 2, subjects with a < EASI 75 response from Baseline or < 4-point improvement from Baseline in WP-NRS (weekly average) will have the option to add topical therapy (except for topical JAK inhibitors) as rescue therapy.

All Periods

Investigators should attempt to limit the first step of rescue therapy to topical medications and escalate to systemic medications only for those subjects who do not respond adequately after at least 7 days of topical treatment. Subjects who receive topical rescue treatment during the study treatment period can continue study drug. If a subject needs rescue treatment with a systemic agent (including but not limited to corticosteroids, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, biologics) or phototherapy, study drug should be permanently discontinued prior to the initiation of rescue systemic agent or phototherapy and subject should be discontinued from the study.

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

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

5.5 Withdrawal of Subjects and Discontinuation of Study

AbbVie may terminate this study prematurely, either in its entirety or at any site. The study may be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study. 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. Advance notice is not required by either party if the study is stopped due to safety concerns.

Subjects can request to be discontinued from participating in the study at any time for any reason. The investigator may discontinue any subject's participation at any time for any reason.

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

- The subject requests withdrawal from study drug or the study.
- The investigator believes it is in the best interest of the subject.
- Abnormal laboratory results or AEs that either meet the criteria for discontinuation of study drug as stated in Section 6.2, or rule out safe continuation of the study drug.
- Serious infection (e.g., sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk with continuation of the study drug.

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- Confirmed diagnosis of deep vein thrombosis (DVT), pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Subject develops any malignancy, except for developing a localized NMSC or a carcinoma in-situ of the cervix if this can be successfully treated at its localization.
- Subject develops a gastrointestinal (GI) perforation (other than due to appendicitis or mechanical injury).
- The subject experiences a serious hypersensitivity reaction without an alternative etiology.
- The subject experiences an anaphylactic reaction or other severe systemic reaction that is related to study drug.
- The subject becomes pregnant while on study drug.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- Subject is significantly non-compliant with study visits/study drug administration.
- Initiation of any prohibited systemic therapy for AD.
- Initiation of phototherapy.
- Treatment with a live (attenuated) vaccine with replicating potential.
- Any subject treated for at least 8 weeks with upadacitinib 30 mg QD with a < EASI 50 response (reduction from Baseline) after rescue with topical corticosteroid treatment for at least 1 week must be discontinued.

Additional requirements related to abnormal laboratory values and selected adverse events of special interest (AESIs) are located in Protocol Section 6.2 (Toxicity Management).

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 described in the protocol to ensure all acceptable mitigation steps have been explored.

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5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Discontinuation of Study Drug

Subjects who prematurely discontinue study drug treatment will be discontinued from study participation entirely.

Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment based on available approved treatment options.

If a subject prematurely discontinues study drug, the procedures outlined for the Premature Discontinuation visit (PD Visit) should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy. In addition, an End of Treatment Follow-up Visit after the last dose of study drug is required to ensure all treatment-emergent AEs/SAEs have been resolved. The 30-day or 12-week follow-up phone call (for subjects on upadacitinib or dupilumab, respectively) following the last dose of study drug will not be required for any subject who initiates commercially available upadacitinib or dupilumab upon the study Completion Visit or Premature Discontinuation visit. The End of Treatment Follow-up Visit is defined as:

- For subjects on upadacitinib, a 30-day follow-up visit (or phone call if a visit is not possible) after the last study drug dose will be completed to determine the status of any new or ongoing AEs/SAEs and concomitant medications.
- For subjects receiving dupilumab, a 12-week follow-up visit (or phone call if a visit is not possible) after the last study drug injection will be completed to determine the status of any new or ongoing AEs/SAEs and concomitant medications.

For subjects who prematurely discontinued study participation, this visit may be a telephone call if a site visit is not possible.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD Visit) should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy. In addition, if subject is willing, a 30-day or 12 week follow-up phone call or visit after the last dose of study drug (for upadacitinib and dupilumab, respectively) may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

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.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

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In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s), and the samples will be destroyed. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Upadacitinib will be taken orally daily, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day, with or without food.

Dupilumab will be administered subcutaneously (SC) at the Baseline visit, followed by SC injection EOW.

Subjects will continue their disease-related concomitant medications therapy as allowed per protocol. AbbVie will not supply any disease-related concomitant medication therapy taken during the course of the study.

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

AbbVie will supply upadacitinib and dupilumab (Table 2). AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Upadacitinib must be stored at controlled room temperature (15° to 25°C/59° to 77°F). Dupilumab must be stored at refrigerated temperature (2° to 8°C/35° to 46°F). Study drug 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 should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of the study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be performed according to instructions from the sponsor and according to local regulations following completion of drug/device accountability procedures.

During the COVID-19 pandemic or geo-political crisis in Ukraine, study drug shipment can be made from the study site to the subject if allowed by local regulations. Refer to the Operations Manual for details on direct-to patient shipment of study drug.

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Table 2. Description of Study Drug

	Investigational Product	Investigational Product	Investigational Product
Investigational product name	Upadacitinib (ABT-494)	Upadacitinib (ABT-494)	Dupilumab pre-filled syringe
Mode/Route of Administration (ROA)	Oral	Oral	SC
Formulation	15 mg	30 mg	200 mg 300 mg
Dosage Form	Extended-release tablets	Extended-release tablets	Solution for injection in pre-filled syringe
Masking	Open-label	Open-label	Open-label
Frequency of administration	QD	QD	Adults: Dupilumab 600 mg (2 × 300 mg dupilumab SC injection) administered at the Baseline visit, followed by dupilumab 300 mg SC injection every other week Adolescents (12 to 17 years of age weighing at least 40 kg): Dose of dupilumab for subcutaneous administration in adolescent subjects 12 to 17 years of age with atopic dermatitis Body weight of subject: 1. 40 to <60 kg: • Initial dose: 400 mg (two 200 mg injections) • Subsequent doses (EOW): 200 mg 2. 60 kg or more: • Initial dose: 600 mg (two 300 mg injections) • Subsequent doses (EOW): 300 mg
Storage Conditions	15° to 25° C	15° to 25° C	2° to 8° C
Manufacturer	AbbVie	AbbVie	Sanofi, Genzyme (Regeneron) or other

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5.8 Randomization/Drug Assignment

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

Randomization for the study is described in Section 4.1. Randomization will be stratified by baseline vIGA-AD categories [3;4] and age categories (12 to < 18; 18 to < 40; ≥ 40 to < 64 years).

The efficacy assessor will remain blinded to each subject's treatment through Week 32. Subjects and other study site personnel will be aware of the subject's treatment assignment. The IRT will provide access to unblinded subject treatment information in the case of medical emergency.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

In Japan, the investigator will record all protocol deviations in the appropriate medical records at the site.

5.10 Data Monitoring Committee

Given that the study is only assessor blinded and no subjects participating in the study will receive placebo, the causality of any AEs reported in the participants can be adequately assessed in the context of upadacitinib or dupilumab treatment. The study team will monitor and evaluate any AEs to identify findings that could put the study participants at risk and then make clinical decisions regarding the study conduct, which could include modification or termination of the study. This can adequately safeguard the participants. Given the above, it is not necessary to implement an independent Drug Monitoring Committee for the conduct of this study.

5.11 Paper Diary Cards for Sites in China Only

For sites in China only, a paper diary card for recording adverse events, concomitant medications, and dosing will be provided at Baseline and subjects will be trained on how to complete the diary cards by site staff during the visit. If subjects require re-training during the study, the site staff will accommodate this requirement.

All subjects should complete their paper diary cards throughout the entire study. Subjects will be instructed to bring their paper diary cards back to the site to be reviewed and collected at each visit,

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including at any visit at which a dose level change may be required. If COVID-19 circumstances warrant a virtual visit, diary cards should be reviewed virtually with the subject and site should collect the paper diary card at the next on-site visit. Subjects will be instructed to record the date and time each dose of study drug is taken, indicating if any doses of study drug are missed.

Subjects will also be instructed to record adverse events symptoms and concomitant medications in the paper diary cards. At each visit, the paper diary cards are to be reviewed by the investigator, assessed for any updates needed, and collected from the subject by study staff. Relevant information will be recorded in existing adverse event, drug administration, and concomitant medication as applicable. At each visit after Baseline, including the Final/Premature Discontinuation Visit, the paper diary cards are to be returned to the site and appropriately filed with the subject's source documents for this study. At each visit after the paper diary card is initially dispensed (except the Final/Premature Discontinuation Visit), the subject will be provided a new diary card.

In case of missing diary card information, or when discrepancies are discovered, site personnel should discuss with the subject and document changes to data in site records and eCRF forms, if applicable. The need for completion of the paper diary card will be reinforced with the subject during study visits, as necessary, by the site personnel.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Product Complaint

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

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

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system

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issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

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 occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event 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 adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they are clinically significant, such as resulting in discontinuation from the study, necessitating therapeutic medical intervention, meeting protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be adverse events. Any clinically significant change from baseline per investigator judgment in the study safety evaluations should be reported as an adverse event.

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

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and/or 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 adverse event.

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

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Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Embolic and/or thrombotic event (non-cardiac, non-CNS)**	Cardiovascular (Cardiac) AE eCRF Myocardial Infarction and Unstable Angina AE eCRF Heart Failure Adverse Event eCRF Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF Embolic and Thrombotic Event (Non-Cardiac, Non-central nervous system [CNS]) eCRF
ALT/AST > 3 ULN	Hepatic Abnormal Laboratory Value Supplemental eCRF Hepatic Supplemental Local Labs eCRF (if applicable) Hepatic Supplemental Procedure eCRF (if applicable)
Serum creatinine > 1.5 × the baseline value and > ULN **Serum creatinine ≥ 2.0 mg/dL**	Renal Abnormal Laboratory Value Supplemental eCRF Renal Supplemental Local Labs eCRF (if applicable) Renal Supplemental Procedure eCRF (if applicable)
Herpes zoster infection	Herpes zoster eCRF
Eczema herpeticum (or the synonymous Kaposi's varicelliform eruption)	Eczema herpeticum eCRF
Retinal detachment	Retinal Detachment AE Supplemental eCRF
Fracture	Bone Fracture AE Supplemental eCRF

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.2 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.

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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 along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 30 days or 5 half-lives, whichever is longer, after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent. If a subject prematurely discontinues study participation and begins commercially available upadacitinib drug (Rinvoq), all adverse events reported by healthcare professionals or the patient, will be captured as postmarketing reports. The 30-Day follow-up phone call following the last dose of upadacitinib study drug during the study will not occur for subjects who begin commercially available upadacitinib drug. Similarly, if a subject prematurely discontinues study participation and begins commercially available dupilumab drug (Dupixent), all adverse events reported by the healthcare professionals or the patient, will be captured as postmarketing reports. The 84-day (12 week) follow-up phone call following the last dose of dupilumab study drug during the study will not occur for subjects who begin commercially available dupilumab drug.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

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SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information) and meets one of the above serious criteria.

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

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

Adverse Events of Special Interest

The following AESIs will be monitored during the study:

- Serious infections
- Opportunistic infections
- Herpes Zoster
- Active Tuberculosis
- Malignancy (all types)
- Anemia
- Neutropenia
- Lymphopenia
- Renal dysfunction
- Hepatic disorder
- Elevated creatine phosphokinase (CPK; adolescents only)
- Adjudicated Gastrointestinal perforations
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
- Adjudicated embolic and thrombotic events (non-cardiac, non-CNS)

In addition to the AESIs listed above, the following adverse events will also be monitored during the study:

- Bone Fracture
- Retinal Detachment
- Hypersensitivity Reactions
- Conjunctivitis

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- Keratitis
- Parasitic (Helminth) Infections
- Arthralgia

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0), which can be accessed at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Moderate (Grade 2): minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL) (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.);
- Severe (Grade 3 - 5):
  - Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
  - Grade 4: Life-threatening consequences; urgent intervention indicated;
  - Grade 5: Death related to AE.

The investigator will use the following definitions to assess the relationship of the adverse event 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.

Recording of Adverse Events Symptoms on the Subject Paper Diary Cards:

For sites in China only, subjects are asked to record adverse event symptoms on the subject paper diary cards (see Section 5.11, Paper Diary Cards for Sites in China Only, for description of paper diary cards).

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Cardiovascular Adjudication Committee

An independent committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular, cerebrovascular, embolic, and thrombotic AEs in a blinded manner as defined by the Cardiovascular Adjudication Committee (CAC) charter. A CAC charter will be prepared separate from the protocol that will describe the objective, scope, frequency, and triggers for data reviews.

Gastrointestinal Perforation Adjudication Committee

An internal gastrointestinal perforation committee will identify and adjudicate adverse events of spontaneous GI perforation. The internal committee will be comprised of at least two gastroenterologists or physicians with appropriate expertise who are independent of the clinical study team and blinded to subject treatment assignments. The committee's primary responsibility is to review potential events of GI perforation and adjudicate against a pre-specified case definition. A separate GI perforation charter will be prepared outside of the protocol and will describe the case definition, procedures, roles, and responsibilities.

Pregnancy

Pregnancy in a study subject is not considered an adverse event. However, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. If a pregnancy occurs in a study subject, information regarding the pregnancy, and the pregnancy outcome, will be collected.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days or 12 weeks after the last study drug administration (for upadacitinib or dupilumab, respectively). Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

Subjects who become pregnant during the study must be discontinued from study drug treatment and the study. (Protocol Section 5.5: Withdrawal of Subjects and Discontinuation of Study).

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 of the site becoming aware of the event.

6.2 Toxicity Management

The toxicity management of the AEs including AESIs consists of safety monitoring (review of AEs on an ongoing basis), and, if applicable, interruption of study drug dosing with appropriate clinical management and/or discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

Serious Infections: Study drug should be interrupted if a subject develops a serious infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. Study drug may be restarted once the serious infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

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

Gastrointestinal Perforation: If a diagnosis of GI perforation is confirmed (other than due to appendicitis or mechanical injury), the subject must be permanently discontinued from study drug.

Major cardiovascular event: For subjects who develop a major cardiovascular event (MACE: acute myocardial infarction, stroke) while on study drug, the investigator should evaluate the benefit/risk of continuation, and discuss with the TA MD whether it is appropriate to continue study drug.

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

Subjects who develop malignancies should be referred to appropriate specialists and managed as per standard of care.

Muscle-related symptoms: If a subject experiences symptoms suggestive of myositis or rhabdomyolysis, consider checking CPK and aldolase with clinical management and/or study drug interruption as deemed appropriate by the investigator.

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

Hypersensitivity: If a systemic hypersensitivity reaction (immediate or delayed) occurs, including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme, administration of study drug should be discontinued immediately and appropriate therapy initiated.

Helminth infection: Patients with pre-existing helminth infections should be treated before initiating study drug. If patients become infected while receiving treatment with study drug and do not respond to anti-helminth treatment, treatment with study drug should be interrupted until infection resolves, at the discretion of the PI.

Conjunctivitis and keratitis related events: Study subjects receiving study drug should be advised to report new onset or worsening eye symptoms to the PI. Subjects dosed with study drug who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis should undergo ophthalmological examination.

Eosinophilic conditions: Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) have been reported with dupilumab in adult patients who participated in the asthma development program. Cases of vasculitis consistent with EGPA have been reported with dupilumab and placebo in adult patients with co-morbid asthma in the chronic rhinosinusitis with nasal polyposis development program. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia.

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COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. Study drug may be restarted if fever is resolved without use of antipyretics for 24 hours and other symptoms improved, or if 5 days have passed since the COVID-19 positive test result (whichever comes last). The COVID-19 eCRF must be completed.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 3 and may require a supplemental eCRF to be completed. For subjects with ongoing local laboratory abnormalities which may require data entry into an eCRF, an additional local lab eCRF related to subsequent laboratory abnormalities is only required if the subject has relevant changes in history (e.g., new onset signs or symptoms) or laboratory values which have returned to normal reference range or its Baseline value followed by subsequent laboratory abnormalities meeting toxicity guidelines (considered a new event). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 3, the repeat testing is to occur as soon as possible.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

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

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Laboratory Parameter	Toxicity Management Guideline
AST or ALT	Interrupt study drug if any of the following scenarios are confirmed by repeat testing of AST/ALT: • ALT or AST > 3 × ULN and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5: • A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • If a creatine phosphokinase (CPK) value is not available, a CPK should be drawn to exclude AST/ALT elevations related to muscle injury • ALT or AST > 3 × ULN along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or new-onset eosinophilia. • ALT or AST > 5 × ULN for more than 2 weeks. If ALT or AST > 8 × ULN, interrupt study drug immediately, repeat testing with a new sample, and if repeat test confirms result contact the TA MD Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA PCR testing performed within 1 week (based on initial elevated value): • ALT> 5 × ULN OR • ALT or AST > 3 × ULN if an alternative cause is not readily identified. A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST. A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices). Within one week of the first episode of a positive HBV DNA PCR test, a hepatologist consultation should occur for recommendation regarding subsequent treatment. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

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Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	If serum creatinine is > 1.5 × the Baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × Baseline value. For the above serum creatinine elevation scenario, complete the appropriate supplemental renal eCRF(s).
Creatine Phosphokinase	If a subject experiences any symptoms suggestive of myositis or rhabdomyolysis, blood for measuring CPK and aldolase levels should be drawn with clinical management as deemed appropriate by the investigator. If confirmed CPK value ≥ 4 × ULN and there are no symptoms suggestive of myositis or rhabdomyolysis, the subject may continue study drug at the investigator's discretion after evaluation. If CPK value ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug and contact AbbVie TA MD. For above CPK elevation scenarios, complete supplemental CPK eCRF.

Elective and Emergency Surgeries

For elective and emergency surgeries the following rules will apply:

- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.
- Elective surgery, and interruption of study drug for such a surgery before the primary endpoint visit has been completed must be discussed with the TA MD and only performed with TA MD approval. If the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and ranked secondary endpoints analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

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The primary analysis will be conducted after all ongoing subjects have completed the Week 16 visit or permanently discontinued Period 1, and all data pertaining to Period 1 are cleaned. This analysis is the final and only analysis for the primary and ranked secondary endpoints.

7.2 Definition for Analysis Populations

The ITT Population of Period 1 (ITT_1 population) consists of all subjects who were randomized at Baseline. The ITT Population of Period 2 (ITT_2 population) consists of all subjects who were randomized at Baseline and continue in Period 2. Subjects will be included in the treatment group to which they are randomized. The ITT Populations will be used for all efficacy analyses.

The Safety Population of Period 1 (Safety_1 population) consists of all subjects who received at least 1 dose of study drug in Period 1. The Safety Population of Period 2 (Safety_2 population) consists of all subjects who received at least 1 dose of study drug in Period 2. The populations will be used to provide a comprehensive summary of safety based on treatment received in Period 1 and Period 2 respectively.

7.3 Handling Potential Intercurrent Events for the Primary and Ranked Secondary Endpoints

The following combined composite variable strategy and treatment policy strategy for intercurrent events (ICEs) handling method will be used:

Subjects will be considered as non-responders after the initiation of rescue medication (composite variable strategy); and the value for the variable of interest is used regardless of treatment discontinuation (treatment policy strategy). No other intercurrent event is considered.

7.4 Statistical Analyses for Efficacy

All primary and secondary endpoints will be analyzed in the ITT_1 population to test the superiority of upadacitinib over dupilumab in Period 1. All efficacy endpoints will be summarized descriptively using ITT_2 population in Period 2. Subjects will be included in the treatment group to which they are randomized.

In Period 1, categorical endpoints will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by vIGA-AD categories (vIGA-AD 3; 4) and age (12 to < 18; 18 to < 40; ≥ 40 to < 64 years). For categorical endpoints, missing values and visits after the rescue will be handled by non-responder imputation (NRI) except for missing values due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random, which will be handled by multiple imputation (NRI-MI).

In Period 2, categorical endpoints will be summarized by counts and percentages, as well as 95% confidence interval (CI) of the percentage. The primary approach to handle missing data is Observed Cases.

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Summary and Analysis of the Primary Endpoints

Analysis of the primary endpoint will be conducted on the ITT_1 population based on treatment as randomized. The difference in the proportion of responders will be used to compare upadacitinib group and dupilumab group using the CMH test, stratified by vIGA-AD categories and age (12 to < 18; 18 to < 40; ≥ 40 to < 64 years). NRI-MI will be the primary approach for handling missing data.

The NRI approach and the multiple imputation approach will be used as the sensitivity analysis of the primary endpoint.

Summary and Analysis of Secondary Endpoints

Summary and Analysis of Ranked Secondary Endpoints

Secondary endpoints will be analyzed in the ranked order as outlined in Section 3.3. All secondary categorical variables will be analyzed using CMH test, stratified by vIGA-AD categories and age (12 to < 18; 18 to < 40; ≥ 40 to < 64 years). NRI-MI will be the primary approach for handling missing data.

Summary and Analysis of Additional Efficacy Endpoints

CMH test will be used to analyze categorical variables stratified by vIGA-AD categories and age (12 to < 18; 18 to < 40; ≥ 40 to < 64 years). NRI-MI will be used for handling missing data.

Subgroup Analysis for Efficacy

The primary endpoints will be analyzed by the following subgroups:

- Baseline vIGA-AD (3; 4),
- Baseline EASI score (< 21; ≥ 21),
- Baseline EASI score (< median; ≥ median), and
- Age (12 to < 18; 18 to < 40; ≥ 40 to < 64 years).

7.5 Statistical Analyses for Safety

The safety analyses will be carried out using the Safety Population and will be based on treatments the subjects actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, and vital signs. Note that missing safety data will not be imputed.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as those that began or worsened in severity after the first dose of study drug and no more than 5 half-lives of the drug after the last dose of study drug. Specifically, 30 days will be used for upadacitinib, and 84 days (12 weeks) will be used for dupilumab. The number and percentage of subjects experiencing TEAEs will be tabulated using system organ class and preferred term, overall and by severity and by relationship to the study drug as assessed by the investigator by the Period using the Safety_1 population and Safety_2 population, respectively. Summaries (including percentages and events per 100 patient years) of TEAEs, AESIs, SAEs, deaths, and AEs leading to discontinuation will be provided in both Periods.

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For laboratory tests and vital signs, mean change from baseline and percentage of subject with evaluations meeting pre-defined Potentially Clinically Important criteria will be summarized in both Periods. For selected lab parameters, a listing of all subjects with any laboratory value above Grade 3 of Common Toxicity Criteria will be provided. Additional details for the safety analysis will be provided in the SAP.

7.6 Statistical Analysis of Optional Biomarker Data

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

7.7 Interim Analysis

No interim analysis is planned for this study.

7.8 Overall Type I Error Control

The statistical comparisons of upadacitinib versus dupilumab for the primary efficacy endpoint and the ranked secondary endpoints will be carried out in the hierarchical order under a 2-sided significance level of 0.05. This means that statistically significant results for the comparison in the higher rank (primary, then ranked secondary endpoints) are necessary to initiate the testing of the next comparison in the lower rank. Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and the family-wised error rate is strongly controlled at 0.05.

7.9 Sample Size Determination

Approximately 880 subjects will be randomized to upadacitinib or dupilumab in a 1:1 ratio. Assuming a response rate of 12% in achieving both EASI 90 and WP-NRS 0/1 at Week 16 in the dupilumab group, this sample size will provide more than 90% power to detect the treatment difference of 17% (upadacitinib versus dupilumab), using a two-sided significant level of 0.05.

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

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

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7.11 Ethical Conduct of the Study

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

7.12 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.

8 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).

9 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.

10 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later; and in the last country where the study was conducted.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
AD	atopic dermatitis
ADL	activities of daily living
AE	Adverse event
AESI	adverse event of special interest
Ag	antigen
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	Absolute neutrophil count
AST	aspartate transaminase
BCG	Bacille Calmette-Guérin
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CTEP	Cancer Treatment Evaluation Program
CXR	chest x-ray
CYP3A	cytochrome P450 3A
DL	detection limit
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture
eow	every other week
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good clinical practice

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GFR	glomerular filtration rate
GI	gastrointestinal
HB	hepatitis B
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	HCV antibody
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
ICEs	intercurrent events
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IFN	interferon
IGA	Investigator's Global Assessment
IL	interleukin
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JAK	Janus kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
MACE	major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
Min	minimum
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer

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NRI	Non-responder imputation
NRI-MI	Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 or any other missing data that can be reasonably assumed to be Missing at Random
OR	odds ratio
PCR	polymerase chain reaction
PD Visit	Premature Discontinuation visit
PDE4	phosphodiesterase type 4
PK	pharmacokinetic
PsA	psoriatic arthritis
PUVA	psoralen and ultraviolet A
QD	once a day
RNA	ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	serious adverse reaction
SC	subcutaneously
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
TB	tuberculosis
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TSLP	Thymic stromal lymphopoietin
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
USPI	United States package insert
UV	Ultra-violet
vIGA-AD	validated Investigator´s Global Assessment for AD
vs.	versus
WBC	white blood cells
WP-NRS	Worst Pruritus-Numerical Rating Scale

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M23-696: A Phase 3b/4 Randomized, Open-label, Efficacy Assessor Blinded Study, Comparing the Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Subjects with Moderate to Severe Atopic Dermatitis (Level-Up)

Protocol Date: 02 May 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and 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 (within one (1) calendar day to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

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APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Medical Affairs
		Medical Affairs
		Statistics

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APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities for the study. The individual activities are described in detail in the Operations Manual (Appendix F).

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Study Activities Table

	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 32	Unscheduled/Premature Discontinuation	12-week follow up Visit/Call (subjects on dupilumab)	30-Day Follow Up Visit/ Call (subjects on upadacitinib)
Activity	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 225			
INTERVIEWS & QUESTIONNAIRES												
Visit Window (+/- days)			3					7				
Informed consent/assent	✓											
Eligibility criteria	✓	✓										
Medical/surgical history	✓	✓										
Alcohol, nicotine, drug history	✓	✓										
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Latent TB risk assessment questionnaire	✓											
Review and document pregnancy avoidance recommendations (for all subjects of childbearing age)		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Patient Reported outcomes: WP-NRS (assessed daily via a handheld ePRO device)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
For China sites only, dispense subject paper diary cards for adverse event symptoms, concomitant therapy, and investigational product administration		✓	✓	✓	✓	✓	✓	✓	✓	✓		
For China sites only, review adverse event symptoms and concomitant therapy assessment from the subject paper diary cards			✓	✓	✓	✓	✓	✓	✓	✓		

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	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 32	Unscheduled/Premature Discontinuation	12-week follow up Visit/Call (subjects on dupilumab)	30-Day Follow Up Visit/ Call (subjects on upadacitinib)
Activity	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 225			
For China sites only, collect subject paper diary cards for adverse event symptoms, concomitant therapy, and investigational product administration			✓	✓	✓	✓	✓	✓	✓	✓		
EXAMINATIONS												
Body weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Height (adult)		✓										
Height (adolescent)	✓	✓			✓		✓		✓	✓		
Tanner staging (adolescent)		✓					✓					
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Physical examination	✓	✓					✓		✓	✓		
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12-Lead ECG	✓											
Chest X-ray	✓											
ASSESSOR BLINDED EXAMINATIONS												
EASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
BSA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

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Activity	Screening Day –35 to Day –1	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8 Day 57	Week 12 Day 85	Week 16 Day 113	Week 20 Day 141	Week 32 Day 225	Unscheduled/Premature Discontinuation	12-week follow up Visit/Call (subjects on dupilumab)	30-Day Follow Up Visit/ Call (subjects on upadacitinib)
vIGA-AD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
LOCAL LABS												
Urine Pregnancy test (for all female subjects of childbearing potential		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense urine pregnancy tests for monthly home testing		✓		✓	✓	✓	✓	✓	✓	✓		
CENTRAL LABS												
Serum pregnancy test (for all female subjects of childbearing potential)	✓											
Central Laboratory Tests Clinical Chemistry, Hematology	✓	✓		✓			✓	✓	✓	✓	✓ PRN for AEs	✓ PRN for AEs
Urinalysis	✓											
TB Test (QuantiFERON TB Gold test [or interferon gamma release assay equivalent such as T-SPOT test] and/or local PPD skin test, if required) If locally required, allow for TB testing every 6 months	✓											
HIV, HBV, and HCV	✓											
Beta-D-Glucan (Japan Only)	✓											
Optional Biomarker: Whole blood (plasma for proteomic and targeted protein investigations)		✓	✓	✓	✓		✓	✓	✓	✓		

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	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 32	Unscheduled/Premature Discontinuation	12-week follow up Visit/Call (subjects on dupilumab)	30-Day Follow Up Visit/ Call (subjects on upadacitinib)
Activity	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 225			
Optional Biomarker: Whole blood (serum for proteomic and targeted protein investigations)		✓	✓	✓	✓		✓	✓	✓	✓		
Optional Biomarker: Skin biopsy lesional		✓		✓			✓		✓			
Optional Biomarker: Skin biopsy non-lesional		✓					✓		✓			
Optional Biomarker: Whole blood DNA		✓										
℞ TREATMENT												
Randomization/drug assignment		✓					✓					
Dispense study drug		✓		✓	✓	✓	✓	✓				
Review and copy investigational product administration information from subject paper diary cards for China sites only and perform study drug reconciliation for all sites			✓	✓	✓	✓	✓	✓	✓	✓	✓	

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APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	10 August 2022
Administrative Change 1 (China Only)	05 December 2022
Administrative Change 2 (China Only)	10 January 2023
Version 1.1 (France Only)	13 January 2023
Version 1.2 (Japan Only)	28 February 2023

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

- To update Sponsor emergency contact information and list of protocol signatories.
- To update current upadacitinib treatment indications in (Section 2.1).
- To add the references for the pivotal studies in atopic dermatitis mentioned in Section 2.1 and Section 2.2 and to add references to another important study information in Section 2.1 per France EC request.
- To align with known AEs, and additional detail for current research based on ORAL surveillance study results (Section 2.2).
- To clarify the estimand definition and the handling rule of the intercurrent events (Section 3.1 and Section 7.3).
- To clarify the primary endpoint (Section 3.2).
- To include additional detail for safety assessments, and Tanner Stage assessments included for adolescent subjects required by regulatory agencies (Section 3.5).
- To include that the permanent discontinuation from the study will be mandatory in any subject who has been treated for at least 8 weeks with upadacitinib 30 mg QD and has not achieved an EASI 50 response from Baseline after rescue with topical corticosteroid treatment for at least 1 week (Section 4.1) per FDA request.
- Figure 1 updated for clarification.
- To clarify the eligibility criteria language to enroll subjects < 64 to ensure no subject 65 or older is enrolled (Section 4.1 and Section 5.1).
- To update eligibility criteria for laboratory values specific to pediatric studies, include detail for COVID-19 which better reflects situation post-pandemic, clarify requirements for serum and urine pregnancy tests, to update prior and concomitant medications, to distinguish between live vaccines with replicating potential and those without, and to clarify contraception recommendations (Section 5.1).

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- To add an eligibility criterion specific to France that requires subjects to be registered with a social security scheme, and to specify that they not fall within the scope of Article L1121-6 or Article L1121-8 of the French Public Health Code (Section 5.1).
- To include the rationale for the collection of race and ethnic origin as part of subject demographics (Operations Manual Section 3.2) per France EC request.
- To update the estimated glomerular filtration rate eligibility criterion (Section 5.1) per German CA request.
- To clarify that topical treatment with emollient should be applied for 7 days before Baseline Visit and throughout the study duration (Section 5.1).
- To clarify that topical anti-infectives, topical antihistamines, and bleach baths are allowed per investigator discretion for the duration of the study (Section 5.3).
- To clarify that females who have experienced menarche, or who are Tanner Stage 3 or higher who have not experienced menarche will be considered to be of childbearing potential and update pregnancy avoidance recommendations (Section 5.2).
- To update prohibited medications and therapy to reflect prohibited medications used in indications currently being studied (Section 5.3).
- To align with currently approved options of live vaccines and to highlight country-specific requirements (Section 5.4).
- To remove language that the AbbVie TA MD may mandate individual subject discontinuation clarify malignancy language and clarify malignancy language (Section 5.5).
- To clarify that for subjects on dupilumab, last dose of dupilumab will be at Week 14 instead of Week 16. Dupilumab dose removed from Week 16 for dupilumab responders because the Week 16 dose would be considered as a Period 2 dose. (Section 5.6).
- To clarify that the 12 week follow up includes the 2 weeks after last dose of dupilumab plus 10 weeks after the Week 16 visit (Section 5.6).
- To align with relevant PK guidelines, removed language that study drug should be taken at approximately the same time each day, with or without food.
- To add the use of subject paper diary cards for sites in China only to collect AE symptoms, concomitant therapy, and IP administration (Section 5.11).
- Included Japan specific details regarding: subject history (Section 5.1), bilateral tubal occlusion/litigation (Section 5.2), live herpes zoster vaccine (Section 5.4 and Operations Manual Section 3.11), protocol deviations (Section 5.9), GCP compliance (Section 7.11), beta-D-glucan testing for pneumocystis jirovecii infection (Appendix D and Operations Manual Section 2.1 & Section 3.13), added section to include information for which safety information is reported in Japan (Operations Manual 5.4). Note that historical height from Japan Protocol Version 1.2 (Operations Manual Section 2.1 & Section 3.9) is no longer required for this study due to the study design.
- To update complaints and adverse events to include adverse events (AEs) known to be related to dupilumab treatment, and clarity that any clinically significant change in the study safety evaluations should be reported as an adverse event (Section 6.1) per FDA request.

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- To add cardiac events, AEs of retinal detachment and bone fracture, clarify that CPK monitoring is optional and update pregnancy protocol AE language (Section 6.1).
- To clarify toxicity management language (Section 6.2).
- Clarified height requirements for adults at Baseline (Appendix D and Operations Manual).
- To update CXR requirements to include clarification to reduce exposure to X-rays in subjects with low TB risk (negative TB testing/assessment) (Appendix D and Operations Manual).
- To clarify when at home pregnancy tests are dispensed (Appendix D and Operations Manual).
- To relabel the Study Activities Table header in Appendix D to include "Week 8" to align with table content rows.
- To update the study activities table to allow for TB testing every 6 months if it is locally required (Appendix D).

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