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Protocol for Study M22-000

Moderate to Severe Atopic Dermatitis: Treat-to-Target, Dose-Flexibility Study of Upadacitinib in Adult Subjects

VERSION:	3.0	DATE:	21 December 2023
SPONSOR:	AbbVie*	PLANNED NUMBER OF SITES:	Approximately 115
ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib	EU CT:	2023-504869-23-00

FULL TITLE: A Phase 3b/4 Randomized, Blinded, Treat-to-Target and Dose-Flexibility Study of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis (Flex-Up)

Incorporating Versions 1.0, 2.0, 3.0 and Administrative Change 1

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1 SYNOPSIS

Title: A Phase 3b/4 Randomized, Blinded, Treat-to-Target and Dose-Flexibility Study of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis (Flex-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, 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, TSLP cytokines that play an important role in the pathogenesis of atopic dermatitis (AD). Upadacitinib has been approved 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 (UC), Crohn's disease (CD), and AD. This study aims to provide descriptive data on the efficacy and safety of dose escalation to upadacitinib 30 mg once daily (QD) and dose reduction to upadacitinib 15 mg QD based on a clinical response after 12 weeks of treatment. This data will inform the clinical management for subjects with moderate to severe AD treated with both approved doses of upadacitinib.
Objective(s) and Endpoint(s):	**Primary Objectives** The primary study objectives are: 1) Sub-Study 1 (SS1): The primary study objective for SS1 is to evaluate the efficacy and safety of dose escalation to upadacitinib 30 mg QD in subjects who do not achieve Eczema Area and Severity Index (EASI) 90 on upadacitinib 15 mg QD after 12 weeks. 2) Sub-Study 2 (SS2): The primary study objective for SS2 is to evaluate the efficacy and safety of dose reduction to upadacitinib 15 mg QD in subjects who achieve EASI 90 on upadacitinib 30 mg QD after 12 weeks. No hypothesis testing will be performed in this study. **Primary Endpoint** The primary endpoint is: • Achievement of EASI 90 at Week 24.

	Secondary Endpoints The secondary endpoints are: • Achievement of EASI 75 / 100 at Week 24. • Achievement of EASI 75 / 90 /100 at Week 12. • Achievement of EASI 90 and Worst Pruritus Numerical Rating Scale (NRS) of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12 and Week 24. • Achievement of validated Investigator´s Global Assessment for AD (vIGA-AD) of 0 or 1 at Week 12. • Achievement of vIGA-AD of 0 or 1 at Week 24. • Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 12. • Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 24. • Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12. • Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 24. • Achievement of an improvement (reduction) from Baseline in Dermatology Life Quality Index (DLQI) ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 12. • Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 24. • Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 12. • Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 24. **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):	Approximately 115 sites globally.
Study Population and Number of Subjects to be Enrolled:	Approximately 454 adult subjects (≥ 18 and < 65 years of age) with moderate to severe AD
Investigational Plan:	This is a Phase 3b/4, randomized, blinded, treat-to-target, dose-flexibility, multi-center study that will evaluate upadacitinib, as monotherapy, in approximately 454 adult subjects (≥ 18 and < 65 years of age) with moderate to severe AD who are candidates for systemic therapy.

	The study is comprised of a 35-day Screening Period, a 12-week double-blind period and a 12-week single-blind period. During the single-blind period, subjects will be blinded to the upadacitinib dose and the EASI score evaluations. After the last study visit, a 30-day 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. Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to enter SS1 to receive oral doses of upadacitinib 15 mg QD at Baseline or SS2 to receive oral doses of upadacitinib 30 mg QD at Baseline. At Week 12, subjects receiving upadacitinib 15 mg QD or upadacitinib 30 mg QD will be reassigned based on their EASI 90 response, which is calculated based on the observed EASI values regardless of the use of rescue medications: • Subjects from SS1 who receive upadacitinib 15 mg QD and achieve a < 90% reduction in EASI (< EASI 90) will be allocated to receive oral doses of upadacitinib 30 mg QD, while those who achieve a ≥ 90% reduction in EASI (≥ EASI 90) will continue to receive oral doses of upadacitinib 15 mg QD. • Subjects from SS2 who receive upadacitinib 30 mg QD and achieve < EASI 90 will continue to receive oral doses of upadacitinib 30 mg QD, while those who achieve ≥ EASI 90 will be allocated to receive oral doses of upadacitinib 15 mg QD. **Rescue Therapy** Starting at Week 4 rescue treatment for AD may be provided, if medically necessary and the following parameter is met: • Subjects achieving a < 50% reduction in EASI (< EASI 50) response at any visit compared to the Baseline EASI score. 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 the subject should be discontinued from the study. Investigators should conduct efficacy and safety assessments (e.g., disease severity scores, safety labs) before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary.
Key Eligibility Criteria:	Key eligibility criteria include: 1. Adult subjects ≥ 18 and < 65 years of age at the Screening Visit.

	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 Worst Pruritus NRS ≥ 4. 5. Candidate for systemic treatment defined as prior use of systemic treatment for AD, OR previous inadequate response to TCS, TCI or PDE-4 inhibitors, OR for whom topical treatments are otherwise medically inadvisable. • Subjects with a prior history of biologic use for AD (dupilumab, tralokinumab, lebrikizumab or nemolizumab) will be capped at 50%.
Study Drug and Duration of Treatment:	Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to receive oral doses of upadacitinib 15 mg or 30 mg QD at Baseline. The study treatment duration will be 24 weeks.
Date of Protocol Synopsis:	21 December 2023

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.[2-6] 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, 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, TSLP cytokines that play an important role in the pathogenesis of atopic dermatitis (AD).

Upadacitinib has been approved 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 (UC), Crohn's disease (CD), and AD.

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, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP),[7,8] 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, Japan, Canada, and the United States.[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 were assessed.

Regarding treatment targets in AD, an extensive group of experienced dermatologists have been working to develop optimized and practical criteria for identifying patients who should receive systemic therapy, including definitions of treatment goals, treatment failure, and disease severity following a modified eDelphi methodology and expert recommendation. As a result of this work, a new minimal disease activity (MDA) concept and criteria and consensus-based recommendations for optimizing the management of AD has been recently published and communicated to the scientific community.[10] Following this new concept, different treatment targets based on the achievement of different outcomes measures are categorized as "moderate" and "optimal" targets and the achievement of "optimal" targets is defined as MDA. Physicians and patients/caregivers should aim for optimal treatment targets to optimize disease control and patient outcomes when possible. In terms of Eczema Area and Severity Index (EASI) score, EASI 90 (or absolute EASI ≤ 3) is the optimal target to achieve.

This study aims to provide descriptive data on the efficacy and safety of dose escalation to upadacitinib 30 mg QD and dose reduction to upadacitinib 15 mg QD based on a clinical response target (EASI 90) after 12 weeks of treatment. This data will inform the clinical management for subjects with moderate to severe AD treated with both approved doses of upadacitinib.

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]

In adults, the recommended dose of upadacitinib is 15 mg or 30 mg QD based on individual patient presentation. A dose of 15 mg is recommended for patients at higher risk of venous thromboembolism, major adverse cardiovascular events (MACE), and malignancy. A dose of 30 mg may be appropriate for patients with high disease burden who are not at higher risk of venous thromboembolism, MACE, and malignancy or patients with an inadequate response to 15 mg. The lowest effective dose to maintain response should be used.[9]

For patients ≥ 65 years of age the recommended dose is upadacitinib 15 mg QD.[9] The above indication and posology correspond to the European Union and may vary within different jurisdictions.

The efficacy and safety of upadacitinib 15 mg and 30 mg QD was assessed in 3 Phase 3 randomized, double-blind, multicentre studies (MEASURE UP 1, MEASURE UP 2 and AD UP)[7,8] in a total of 2584 subjects (12 years of age and older). 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, 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 (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, 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 fractures, and some laboratory abnormalities have been observed in patients receiving JAK inhibitors including upadacitinib.

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

In ORAL Surveillance, a post-approval safety study in RA patients 50 years of age and older with at least 1 cardiovascular risk factor, higher rates of malignancies (excluding NMSC), MACE (cardiovascular death, myocardial infarction, and stroke), thrombosis (overall thrombosis, deep vein thrombosis [DVT], and pulmonary embolism), and all-cause mortality were seen with a different JAK inhibitor, tofacitinib, versus TNF blockers.[11] These higher rates were primarily observed in patients 65 years of age and older, patients with a history of atherosclerotic cardiovascular disease, and patients with other cardiovascular risk factors (such as 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 potentially 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 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.

The benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined. For further details, please see findings from completed studies, including safety data in the current upadacitinib Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary Objective

The primary study objectives are:

1. Sub-Study 1 (SS1): The primary study objective for SS1 is to evaluate the efficacy and safety of dose escalation to upadacitinib 30 mg QD in subjects who do not achieve EASI 90 on upadacitinib 15 mg QD after 12 weeks.
2. Sub-Study 2 (SS2): The primary study objective for SS2 is to evaluate the efficacy and safety of dose reduction to upadacitinib 15 mg QD in subjects who achieve EASI 90 on upadacitinib 30 mg QD after 12 weeks.

No hypothesis testing will be performed in this study.

The estimand corresponding to the primary endpoint is defined as:

- The proportion of subjects who achieve EASI 90 at Week 24, regardless of treatment discontinuation, with upadacitinib treatments (upadacitinib 15 mg or 30 mg QD) in adult subjects with moderate to severe AD.

Additional Objective

- To generate evidence on patient impact (patient reported outcomes [PROs]) with upadacitinib treatment based on a clinical response target (EASI 90) (Treat-to-Target).

This study will generate descriptive data that will provide information regarding:

- Efficacy and safety of dose escalation to upadacitinib 30 mg QD in subjects that did not achieve EASI 90 on upadacitinib 15 mg QD after 12 weeks.
- Efficacy and safety of dose reduction to upadacitinib 15 mg QD in subjects that achieve EASI 90 on upadacitinib 30 mg QD after 12 weeks.
- The effect of a treat-to-target approach based on EASI 90 response for subjects' reported itch, sleep, emotional health, and quality of life [QoL].

3.2 Primary Endpoint(s)

The primary endpoint is:

- Achievement of EASI 90 at Week 24.

3.3 Secondary Endpoint(s)

The secondary endpoints are:

- Achievement of EASI 75 / 100 at Week 24.
- Achievement of EASI 75 / 90 / 100 at Week 12.
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12 and Week 24.
- Achievement of a vIGA-AD of 0 or 1 at Week 12.
- Achievement of vIGA-AD of 0 or 1 at Week 24.
- Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 12.
- Achievement of an improvement (reduction) in Worst Pruritus NRS ≥ 4 for subjects with Worst Pruritus NRS ≥ 4 at Baseline at Week 24.

- Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 12.
- Achievement of Worst Pruritus NRS of 0 or 1 for subjects with Worst Pruritus NRS > 1 at Baseline at Week 24.
- Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 12.
- Achievement of an improvement (reduction) from Baseline in DLQI ≥ 4 for subjects with DLQI ≥ 4 at Baseline at Week 24.
- Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 12.
- Achievement of DLQI 0/1 for subjects with DLQI > 1 at Baseline at Week 24.

3.4 Additional Efficacy Endpoints

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

Additional Efficacy Endpoints are:

- Experience of a loss of response after Week 12 until Week 24 (defined as a loss of at least 50% of the EASI improvement gained from Baseline to Week 12) among subjects who had an EASI 90 response at Week 12.
- Achievement of EASI score < 7 / < 3 / < 1.
- Achievement of Worst Pruritus NRS of 0 for subjects with Worst Pruritus NRS >0 at Baseline.
- Achievement of an improvement (reduction) in Patient Oriented Eczema Measure (POEM) ≥ 4 from Baseline for subjects with POEM ≥ 4 at Baseline.
- Achievement of POEM ≤ 2 / = 0 for subjects with POEM > 2 / > 0 at Baseline, respectively.
- Achievement of POEM Itch item score of 0 for subjects with POEM Itch item score >0 at Baseline.
- Achievement of POEM Sleep item score of 0 for subjects with POEM Sleep item score > 0 at Baseline.
- Change and percent change from Baseline in Patient Global Impression of Severity (PGIS).
- Achievement of "Minimal" or "Absent" on the PGIS for subjects who are "Mild" or worse on the PGIS at Baseline.
- Achievement of "Absent" on the PGIS for subjects who are "Minimal" or worse on the PGIS at Baseline.
- Change and percent change from Baseline in Patient Global Impression of Treatment (PGIT).
- Achievement of "Extremely satisfied" or "Very satisfied" on the PGIT for subjects who are "Somewhat satisfied" or worse on the PGIT at Baseline.

- Achievement of "Extremely Satisfied" on the PGIT for subjects who are "Very satisfied" or worse on the PGIT at Baseline.
- Achievement of an improvement (reduction) in Atopic Dermatitis Impact Scale (ADerm-IS) Sleep ≥ 12 from Baseline for subjects with ADerm-IS Sleep ≥ 12 at Baseline.
- Achievement of an improvement (reduction) in ADerm-IS Emotional State ≥ 11 from Baseline for subjects with ADerm-IS Emotional State ≥ 11 at Baseline.
- Achievement of an improvement (reduction) in ADerm-IS Daily Activities ≥ 14 from Baseline for subjects with ADerm-IS Daily Activities ≥ 14 at Baseline.
- Achievement of ADerm-IS Sleep ≤ 3 / = 0 for subjects with ADerm-IS Sleep > 3/> 0 at Baseline, respectively.
- Achievement of ADerm-IS Daily Activities ≤ 2 /= 0 for subjects with ADerm-IS Daily Activities > 2/> 0 at Baseline, respectively.
- Achievement of ADerm-IS Emotional State ≤ 2 / = 0 for subjects with ADerm-IS Emotional State > 2/> 0 at Baseline, respectively.
- Achievement of an improvement (reduction) in Atopic Dermatitis Symptom Scale (ADerm-SS) Skin Pain ≥ 4 from Baseline for subjects with ADerm-SS Skin Pain ≥ 4 at Baseline.
- Achievement of ADerm-SS Skin Pain ≤ 1 / = 0 for subjects with ADerm-SS Skin Pain > 1/> 0 at Baseline, respectively.
- Achievement of an improvement (reduction) in ADerm-SS 7-item total symptom score (TSS-7) ≥ 28 from Baseline for subjects with ADerm-SS TSS-7 ≥ 28 at Baseline.
- Achievement of ADerm-SS TSS-7 ≤ 11 / ≤ 1 for subjects with ADerm-SS TSS-7 > 11 / > 1 at Baseline, respectively.
- Achievement of EASI 75 / 90, for subjects who experienced an inadequate response to previous treatment with dupilumab for AD as reported by the investigator
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1, for subjects with Worst Pruritus NRS > 1 at Baseline and experienced an inadequate response to previous treatment with dupilumab for AD as reported by the investigator.
- Achievement of EASI 75 / 90, for subjects who were previously treated with dupilumab for AD.
- Achievement of EASI 90 and a Worst Pruritus NRS of 0 or 1, for subjects with Worst Pruritus NRS > 1 at Baseline and were previously treated with dupilumab for AD.
- For subjects participating in the Wearable Tool Substudy:
    - Change from Baseline in average nightly nocturnal scratch: total scratch time and number of scratch events.
    - Change from Baseline in the following sleep parameters: total sleep time, wake after sleep onset, sleep efficiency, and sleep onset latency.

For PROs that are assessed daily (Worst Pruritus NRS, ADerm-SS, ADerm-IS), the associated endpoints will also be analyzed daily for the initial 28 days of the double-blind treatment period and the initial 28 days of the single-blind treatment period.

3.5 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.

3.6 Biomarker Research Endpoints

Optional biospecimens (blood, plasma, serum, and PBMC) 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, and/or metabolites, either free or in association with particular cell types. In addition, pharmacogenetic DNA samples may be collected for exploratory analysis of genetic factors contributing to disease pathology and subject's response to study treatment. The biomarker research results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Appendix F, Section 3.8.

No biomarker samples will be collected in China.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b/4, randomized, blinded, treat-to-target, dose-flexibility, multi-center study that will evaluate upadacitinib, as monotherapy, in approximately 454 adult subjects (≥ 18 and < 65 years of age) with moderate to severe AD who are candidates for systemic therapy.

The study is comprised of a 35-day Screening Period, a 12-week double- blind period and a 12-week single-blind period. During the single-blind period, subjects will be blinded to the upadacitinib dose and EASI score evaluations.

The study treatment duration will be 24 weeks.

After the last study visit, a 30-day 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.

Subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to enter SS1 to receive oral doses of upadacitinib 15 mg QD at Baseline or SS2 to receive oral doses of upadacitinib 30 mg QD at Baseline.

- SS1:
  - Subjects randomized to enter the SS1 at Baseline will receive oral doses of upadacitinib 15 mg QD during the 12-week double-blind period.

- At Week 12, subjects from SS1 receiving upadacitinib 15 mg QD will be reassigned based on their EASI response, which is calculated based on the observed EASI values regardless of the use of rescue medications:
  - Subjects achieving a < 90% reduction in EASI (< EASI 90) will be allocated to receive oral doses of upadacitinib 30 mg QD. This constitutes the Study Cohort 1 (SC1).
  - Subjects achieving a ≥ 90% reduction in EASI (≥ EASI 90) will continue to receive oral doses of upadacitinib 15 mg QD. This constitutes the Study Cohort 2 (SC2).

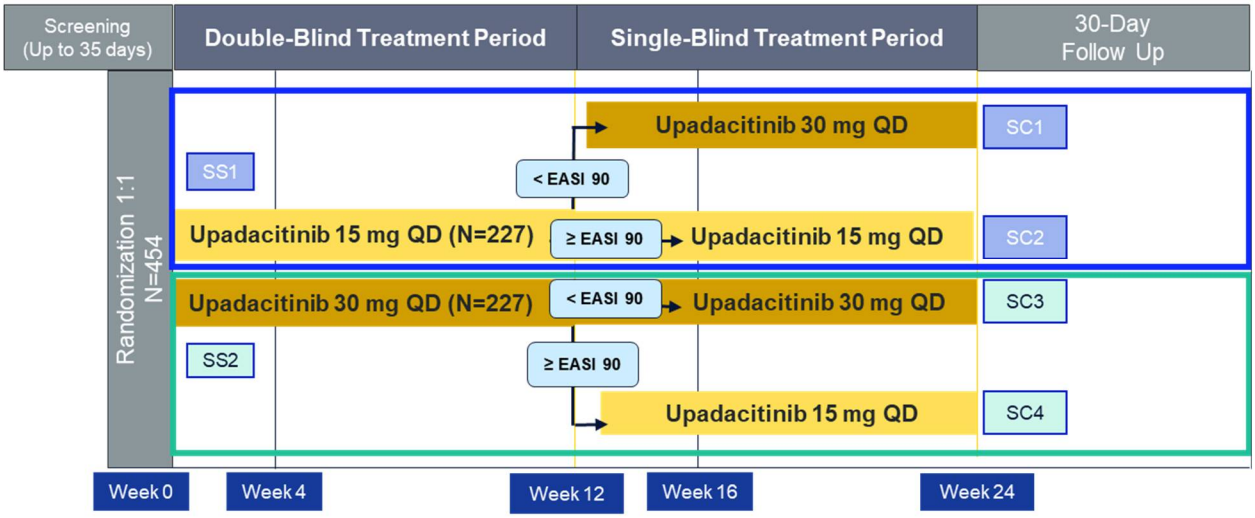
- SS2:
  - Subjects randomized to enter SS2 at Baseline will receive oral doses of upadacitinib 30 mg QD during the 12-week double-blind period.
  - At Week 12, subjects from SS2 receiving upadacitinib 30 mg QD will be reassigned based on their EASI response, which is calculated based on the observed EASI values regardless of the use of rescue medications:
    - Subjects achieving < EASI 90 will continue to receive oral doses of upadacitinib 30 mg QD. This constitutes the Study Cohort 3 (SC3).
    - Subjects achieving ≥ EASI 90 will be allocated to receive oral doses of upadacitinib 15 mg QD. This constitutes the Study Cohort 4 (SC4).

The final and only database lock will occur at the end of the study.

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

See Section 5 for information regarding eligibility criteria. See also Section 5.4, Rescue Therapy for further details on allowed rescue.

Figure 1. Study Schematic



EASI = Eczema Area and Severity Index; QD = once daily; SS1 = Sub-Study 1; SS2 = Sub-Study 2; SC1 = Study Cohort 1; SC2 = Study Cohort 2; SC3 = Study Cohort 3; SC4 = Study Cohort 4

Note: The study will be stratified by Baseline vIGA-AD categories (3; 4) and prior use of dupilumab (yes; no).

Wearable Tool Substudy

Subjects in select countries and sites where the digital health technology device is deployed and available will participate in a Wearable Tool Substudy, using ADAM (ADvanced Acousto-Mechanic) sensor made by Sibel Health. Subjects participating in this substudy will wear a digital tool on the back of their dominant hand while sleeping for 7 nights prior to the Baseline visit, then for specified weeks during the study. The tool will collect data reflecting the subject's nocturnal scratch and sleep parameters by Bluetooth signal to a provided tablet, which transfers the data by cellular network to a secure cloud-based server. Enrollment will be capped at 90 subjects.

The ADAM Sensor, manufactured by Sibel, collects actigraphy data through raw acoustic signals and mechanical movement to quantify nocturnal scratch duration and intensity. The sensor offers streaming ability through the mobile ADAM application and is integrated with the vendor's cloud and web application. Data, which may be in raw/preliminary format, collected by the vendor, will be accessible to the clinical investigator. The digital tool is for Research Use Only and will not be used for diagnosis or treatment. All source data will be retained by AbbVie and the investigators per 21 CFR 312.62(b), 812.140(a)(3), and ICH-GCP 8.1.

4.2 Discussion of Study Design

Choice of Control Group

A dose comparison concurrent control was selected for this study.

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. 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 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 adult AD population with moderate to severe disease activity appropriate for systemic therapies. Adult subjects ≥ 18 and < 65 years of age 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).

The dose selection was informed by the 2 doses (upadacitinib 15 mg and 30 mg QD) studied in the pivotal trials for AD and approved for the treatment of moderate to severe AD in several jurisdictions, including but not limited to the European Union, Japan, Canada, and United States. Both doses showed a positive benefit-risk profile, and the objective of this study is to generate data that will help inform the more appropriate use of both approved doses.

All currently available Pharmacokinetic(s), Pharmacodynamic, Safety and Efficacy Data from upadacitinib studies were used to support the selection of these doses.

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). Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Adult subjects ≥ 18 and < 65 years of age at the Screening Visit. Subjects must be able to understand and willing to adhere to all protocol requirements and 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. If the subject is 64 years old at the Screening Visit, the subject must also not turn 65 years old at or after Baseline or before completing study participation.

Atopic Dermatitis Disease History

- 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 Worst Pruritus NRS ≥ 4. Note: The Baseline weekly average of daily Worst Pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline Visit. A minimum of 4 daily scores out of the 7 days is needed.
- 5. Candidate for systemic treatment defined as prior use of systemic treatment for AD, OR previous inadequate response to TCS, TCI or PDE-4 inhibitors, OR for whom topical treatments are otherwise medically inadvisable.
  - Subjects with a prior history of biologic use for AD (dupilumab, tralokinumab, lebrikizumab or nemolizumab) will be capped at 50%.
- 6. Wearable Tool Substudy only: Subjects must not have active AD on the back of their dominant hand where the tool will be worn at screening. Subjects with this finding may participate in the study as a whole if all other eligibility criteria are met.

Laboratory Assessments

- 7. **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;
  - 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.

Subject History

- 8. Subject is judged to be in good health as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, and a 12-lead electrocardiogram (ECG) performed during Screening. In addition, a chest x-ray (CXR) (or computed tomography equivalent if performed outside study setting) is required if requested per local guidelines and for subjects with a positive purified protein derivative (PPD) and/or QuantiFERON-TB Gold Plus test and/or one or more "yes" response on Part I of the Tuberculosis (TB) Risk Assessment Questionnaire.

- 9. Subject must have no current or past history of infection including:
  - 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 TB or meet TB exclusionary parameters (specific requirements for TB testing are provided in the operations manual [Appendix F]);
  - Japan only: Positive result of beta-D-glucan (screening for Pneumocystis jirovecii infection) or two consecutive indeterminate results of beta-D-glucan during the Screening Period;
  - 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, 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 since the COVID-19 positive test result (whichever comes last). Subjects may be rescreened if judged to be in good general health, as determined by the investigator based upon the medical history and physical examination.
- 10. Subjects must not have evidence of:
  - Hepatitis B virus (HBV): hepatitis B surface antigen (HBs Ag) positive (+) test or detectable 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);
  - Hepatitis C virus (HCV): detectable HCV ribonucleic acid (RNA) in any subject with anti-HCV antibody (HCV Ab).
- 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;
  - 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. Subject must not have a history of clinically significant (per investigator judgment) drug or alcohol abuse within the last 6 months.
- 13. There must be 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.
- 14. France only: 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).
- 15. Wearable Tool Substudy only: Subjects must not have a history of pre-existing sleep disorders, including insomnia, obstructive sleep apnea, restless leg syndrome or currently on prescription sleep medications to participate in the sleep assessment portion of the study. Subjects with these histories may participate in the study as a whole if all other eligibility criteria are met.

Contraception

- 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).
- 17. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from Study Day 1 (or earlier as defined in Section 5.2) through at least 30 days after the last dose of study drug (local practices may require 2 methods of birth control) (refer to Section 5.2 for more detail on contraception). Female subjects of non-childbearing potential do not need to use birth control.
- 18. Females must not be **pregnant, breastfeeding, or considering becoming pregnant** during the study and for approximately 30 days after the last dose of study drug.

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®], or deucravacitinib [Sotyktu®]).
- 20. Subjects must not have used the following AD treatments within the specified timeframe prior to Baseline Visit:
  - Systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)- inhibitors, IFN-γ, mycophenolate mofetil within 3 weeks;
  - Topical treatments including but not limited to TCS, TCIs, or topical PDE-4 inhibitors within 7 days;
  - Targeted biologic treatments within 6 weeks; or
  - Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 3 weeks.
- 21. Subject must not have been treated with **any investigational drug** of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study.
- 22. 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 in Section 5.3 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.
- 23. Subject must not have received any live vaccine with replicating potential within 28 days (or longer if required locally) prior to the first dose of study drug or have expected need of live vaccine with replicating potential during study participation including at least 30 days (or longer if required locally) after the last dose of study drug. 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.

Females, of Childbearing Potential

A female who does not meet the criteria above for females of non-childbearing potential is considered to be a female of childbearing potential.

- Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days after the last dose of study drug. Contraception methods must be continued while taking study drug and for at least 30 days after the last dose of study drug. Females must commit to using a contraceptive method listed below that is highly effective (with a failure rate of < 1% per year, when used consistently and correctly):
    - 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 (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

    If required per local regulations, a barrier method (preferably a male condom with or without spermicide; other barrier methods include female condom OR cap, diaphragm *or* sponge with spermicide) should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to the 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.
- 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.

5.3 Prohibited Medications and Therapy

Biologic Therapies

Subjects must have discontinued biologic therapies with immunosuppressive potential at least 6 weeks prior to the first dose of study drug.

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
- Golimumab
- Infliximab
- Ixekizumab
- Lebrikizumab
- Natalizumab
- Nemolizumab
- Risankizumab
- Rituximab
- Secukinumab

- Tocilizumab
- Tralokinumab
- Ustekinumab
- Vedolizumab

Other Non-Biologic Systemic Therapy

Concomitant treatment with systemic non-steroidal 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, Rescue Therapy for further details on allowed rescue.

Corticosteroids

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

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

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

CYP3A = cytochrome P450 3A

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.

Topical Therapy

No topical treatments for AD should be started for the duration of the treatment with study drug except for rescue treatment (see Section 5.4, Rescue Therapy). This includes but is not limited to calcineurin inhibitors, corticosteroids, phosphodiesterase-4 inhibitors and prescription moisturizers. Topical emollient treatments are allowed.

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 Therapeutic Area Medical Director (TA MD) or Therapeutic Area Scientific Director (TA SD).

Other Medications Prohibited during the Study

- Oral and topical JAK inhibitors, including but not limited to commercial upadacitinib (Rinvoq®), tofacitinib (Xeljanz®), ruxolitinib (Jakafi® or Opzelura®), baricitinib (Olumiant®), peficitinib (Smyraf®), abrocitinib (Cibinqo®), filgotinib (Jyseleca®), 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 moderate to severe 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 daily on the subject paper diary cards (see Section 5.12).

Rescue Therapy

Starting at Week 4 rescue treatment for AD may be provided, if medically necessary and the following parameter is met:

- Subjects achieving a < 50% reduction in EASI (< EASI 50) response at any visit compared to the Baseline EASI score.

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

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 longer if required locally) after the last dose of study drug. Examples of live vaccines with replicating potential include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- 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/monkeypox vaccine capable of replicating (ACAM2000®);
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid (oral).

If the live herpes zoster vaccine is to be administered (should 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 (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.

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). 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.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of upadacitinib on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of upadacitinib, when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with AD and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

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 their site if they have 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 infections (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.
- Confirmed diagnosis of deep vein thrombosis (DVT), pulmonary embolus (PE) 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.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix if this can be successfully treated at its localization
- Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injury).
- The subject experiences a serious hypersensitivity reaction without an alternative etiology.
- 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.
- The investigator determines the subject is significantly non-compliant with the study.
- Initiation of any prohibited systemic therapy for AD.
- Initiation of phototherapy.
- Treatment with a live (attenuated) vaccine with replicating potential.

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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.

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

During the study drug dosing period, for a subject with confirmed (viral test positive) or suspected COVID-19 infection, the timing of next administration of study drug or possibility of premature discontinuation would be at the discretion of the investigator. Follow Section 5.6 for subjects who discontinued study drug.

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

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

Discontinuation of Study Drug

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

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

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, a 30-Day Follow-up Visit after the last dose of study drug is required to ensure all treatment-emergent AEs/SAEs have been resolved. For subjects who prematurely discontinued study participation, this visit may be a telephone call if a site visit is not possible. A follow-up phone call following the last dose of upadacitinib during the study will not occur for subjects who begin commercially available upadacitinib.

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 the subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved. The follow-up phone call following the last dose of upadacitinib during the study will not occur for subjects who begin commercially available upadacitinib.

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.

If a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s), 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

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug

	Investigational Product	Investigational Product
Investigational product name	upadacitinib	upadacitinib
Mode/Route of Administration (ROA)	Oral	Oral
Formulation	15 mg	30 mg
Dosage Form	Extended-release tablets	Extended-release tablets
Masking	Blinded	Blinded
Frequency of administration	QD	QD
Manufacturer	AbbVie	AbbVie

QD = once daily

Upadacitinib will be taken orally once daily, beginning on Day 1 (Baseline) and can be taken with or without food. Upadacitinib should be taken whole and should not be split, crushed, dissolved, etc. If subjects should forget to take upadacitinib at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 10 hours before their next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

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

AbbVie will provide upadacitinib. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

AbbVie will not supply drug other than upadacitinib. Subjects will continue their AD disease-related concomitant medications therapy as allowed per protocol. AbbVie will not supply any AD disease-related concomitant medication therapy taken during the study.

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.

During the COVID-19 pandemic, 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 (Appendix F).

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 according to instructions from the Sponsor according to local regulations following completion of drug accountability procedures.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie. Subjects in the study will be randomized in a 1:1 ratio to one of the 2 treatment groups:

- Upadacitinib 15 mg QD
- Upadacitinib 30 mg QD

The study will be stratified by Baseline vIGA-AD categories (3; 4) and prior use of dupilumab (yes; no).

IRT will provide the appropriate study drug kit number(s) to dispense to each subject. Returned study drug must not be re-dispensed to any subject.

All AbbVie personnel with direct oversight of the conduct and management of the trial (apart from the AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment through Week 12. After Week 12, the subject will be blinded to the upadacitinib dose they will receive.

Blinding of Investigational Product

During the 12-week double-blind period, study sites and subjects will remain blinded. During the single blind period, only the subjects will be blinded to the upadacitinib dose and the EASI score evaluations. In order to maintain the blind, the upadacitinib tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of medical emergency.

In the event of a medical emergency that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting technical support via either phone (preferred) or email.

In the event that the blind is broken before notification to the AbbVie Therapeutic Area Medical Director (TA MD), we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on the appropriate eCRF.

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, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying the independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable by local requirements), and AbbVie.

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

5.10 Data Monitoring Committee

Given no subjects participating in the study will receive placebo or other active comparators, the causality of any AEs reported in the participants can be adequately assessed in the context of upadacitinib 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 Data Monitoring Committee for the conduct of this study.

5.11 Publication Policy

AbbVie as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final clinical study report of the multicenter study except as agreed with the sponsor.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

Investigators are NOT employed by the organization sponsoring the study. There is an agreement between investigators and the sponsor (or its agents) that restricts the investigator's rights to discuss or publish study results after the study is completed.

AbbVie requests that any investigator or institution that plans on presenting/publishing results, provide written notification of their request 60 days prior to their presentation/publication. AbbVie requests that no presentation/publication will be instituted until 12 months after a study is completed or after the first presentation/publication, whichever occurs first. A delay may be proposed for a presentation/publication if AbbVie needs to secure patent or proprietary protection.

5.12 Paper Diary Cards for Sites in China Only

For sites in China only, a paper diary card will be provided to subjects. Subjects will be trained on how to complete the diary cards by site staff. If subjects require re-training during the study, the site staff will accommodate this requirement.

All subjects should complete their paper diary cards until completion of the study. Subjects will be instructed to bring their paper diary cards back to the site to be reviewed and collected at each visit, 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 the site should collect the paper diary card at the next onsite visit. Subjects will be instructed to record the date and time each dose of study drug is taken, indicating if any doses of study drugs are missed.

Subjects will also be instructed to record AE 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 AE, drug administration, and concomitant medication forms in the eCRF as applicable. At each visit after the paper diary card is initially dispensed, including the final/PD 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/PD Visit), the subject will be provided with 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 forms and eCRFs, 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 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 AEs 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: Upadacitinib

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "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 AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

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

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

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

Adverse Event	Supplemental Form
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Embolic and/or thrombotic event (non-cardiac, non- central nervous system [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-CNS) eCRF
Herpes Zoster Infection	Herpes Zoster AE eCRF
ALT/AST > 3 ULN	Hepatic Abnormal Laboratory Value Supplemental eCRF Hepatic Supplemental Local Labs eCRF (if applicable) Hepatic Supplemental Procedure eCRF (if applicable)
Serum creatinine > 1.5 × the baseline value and > ULN **Serum creatinine ≥ 2.0 mg/dL**	Renal Abnormal Laboratory Value Supplemental eCRF Renal Supplemental Local Labs eCRF (if applicable) Renal Supplemental Procedure eCRF (if applicable)
Eczema herpeticum (or the synonymous Kaposi's varicelliform eruption)	Eczema herpeticum eCRF
Malignancy	Malignancy eCRF
Hypersensitivity Reactions	Hypersensitivity Reactions eCRF
Retinal detachment	Retinal detachment eCRF
Fracture	Fracture eCRF

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information [Appendix F]):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug, only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). 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 (Rinvoq), all AEs reported by healthcare professionals or the patient will be captured as post-marketing 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.

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

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 SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation 536/2014.

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 adverse events of special interest (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;
- Adjudicated GI perforations;
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]); and
- Adjudicated embolic and thrombotic events (non-cardiac, non-CNS).
- Fractures
- Retinal detachment

Cardiovascular Adjudication Committee

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

Gastrointestinal Perforation Adjudication Committee

An internal GI perforation committee will identify and adjudicate AEs of spontaneous GI perforation. The internal committee will be comprised of at least 2 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.

Adverse Event Severity and Relationship to Study Drug

Investigators 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 self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
  - Grade 4: Life-threatening consequences; urgent intervention indicated;
  - Grade 5: Death related to AE.

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

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

Pregnancy

While not an AE, 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 outcome will be collected.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration. 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 study (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 after the site becomes aware of the event.

Recording of Adverse Event Symptoms on the Subject Paper Diary Cards

For sites in China only, subjects will be instructed to record AE symptoms on the subject paper diary cards (see Section 5.12, Paper Diary Cards for Sites in China Only, for description of paper diary cards).

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 infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

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

Gastrointestinal Perforation: If a diagnosis of gastrointestinal 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, and discuss with the TA MD, whether it is appropriate to continue study drug.

Malignancy: Subjects who develop malignancy other than localized 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 (DVT), pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

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 laboratory abnormalities which require data entry into an eCRF, an additional 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.

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).

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 x Baseline value. For the above serum creatinine elevation scenario, complete the appropriate supplemental renal eCRF(s).

ALC = Absolute lymphocyte count; ALT = alanine transaminase; ANC = Absolute neutrophil count; AST = aspartate transaminase; DNA = deoxyribonucleic acid; eCRF = electronic case report form; HBc Ab+ = Hepatitis B core antibody positive; HBs Ab = Hepatitis B surface antibody; HBV = Hepatitis B virus; INR = international normalized ratio; OR = odds ratio; PCR = Polymerase chain reaction; TA MD = Therapeutic Area Medical Director; ULN = upper limit of normal

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, will not be allowed during the study until the primary endpoint has been assessed (Week 24). If elective surgery is considered prior to the primary endpoint visit (Week 24), it must be discussed with the TA MD and 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.

6.3 Other Safety Data Collection

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

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 secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

7.2 Definition for Analysis Populations

The Intent to Treat (ITT) Populations for the efficacy analyses are defined as:

- ITT Population of SS1 in the double-blind period (ITT_1_SS1 Population) includes all subjects who are randomized into SS1.
- ITT Population of SS1 in the single-blind period (ITT_2_SS1 Population) includes all subjects who are randomized into SS1 at Baseline and continued into the single-blind period.
- ITT Population of SS2 in the double-blind period (ITT_1_SS2 Population) includes all subjects who are randomized into SS2.
- ITT Population of SS2 in the single-blind period (ITT_2_SS2 Population) includes all subjects who are randomized into SS2 at Baseline and continued into the single-blind period.

The Safety Populations for the safety analyses are defined as:

- Safety Population of SS1 in the double-blind period (Safety_1_SS1 Population) consists of all subjects who are randomized into SS1 and received at least 1 dose of study drug in the doubleblind period.
- Safety Population of SS1 in the single-blind period (Safety_2_SS1 Population) consists of all subjects who received at least 1 dose of study drug in the single-blind period of SS1.
- Safety Population of SS2 in the double-blind period (Safety_1_SS2 Population) consists of all subjects who are randomized into SS2 and received at least 1 dose of study drug in the doubleblind period.
- Safety Population of SS2 in the single-blind period (Safety_2_SS2 Population) consists of all subjects who received at least 1 dose of study drug in the single-blind period of SS2.
- Safety Population for all upadacitinib treatment (ALL_UPA Population) consists of all subjects who received at least 1 dose of upadacitinib in the study.

These populations will be used to provide a comprehensive summary of safety based on treatment received regardless of randomization.

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

For all endpoints, no intercurrent event will be considered in the primary approach (treatment strategy policy), i.e., all observed data will be included in the primary analysis.

7.4 Statistical Analyses for Efficacy

The efficacy analyses will be summarized in the ITT Populations descriptively and no statistical testing will be performed in this study.

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

The primary approach for efficacy summary is As Observed (AO).

Summary and Analysis of the Primary Endpoint

The primary endpoint will be summarized in the ITT_2_SS1 and ITT_2_SS2 Populations by counts and percentages, as well as the 95% CIs of the percentage. The AO approach will be used as the primary approach.

Sensitivity analyses of the primary endpoint will be conducted. The primary endpoint will be summarized using the Multiple Imputation (MI) to handle missing data. The details will be specified in the SAP.

Summary and Analysis of Secondary Endpoints

Summary of the secondary efficacy endpoints will be conducted using the ITT Populations with the treatment as randomized. Categorical variables will be summarized by counts and percentages, as well as 95% CIs of the percentage. The AO approach will be used.

Summary and Analysis of Additional Efficacy Endpoints

Additional endpoints, as described in the Section 3.4, will also be summarized using the AO approach. The analysis details will be provided in the SAP.

Subgroup Analysis for Efficacy

The primary endpoints, as described in Section 3.1, will be also summarized by the following subgroups using the AO approach:

- Baseline vIGA-AD (3; 4),
- Baseline EASI score (<21; ≥21), and
- Baseline EASI score (<median; ≥median).

7.5 Statistical Analyses for Safety

The safety analyses will be summarized in the double-blind period, single-blind period, and across study periods by the upadacitinib doses, based on the Safety_1_SS1 and Safety_1_SS2 Populations, Safety_2_SS1 and Safety_2_SS2 Populations, and ALL_UPA Population, respectively.

Safety will be assessed by AEs, physical examination, laboratory assessments, and vital signs. Note that missing safety data will not be imputed. Analysis details will be specified in the SAP. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs in each period are defined as those that began or worsened in severity after the first dose of study drug in each period and up to the minimum of the end date of each period and 30 days after the last dose of the study drug in each period. The number and percentage of subjects experiencing TEAEs in each period

and across study periods by the upadacitinib doses will be tabulated using the MedDRA SOC and PT, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including number of subjects, percentages and events per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation, and AESI will be provided in each period and across study periods by the upadacitinib doses as well.

For laboratory and vital signs, mean change from Baseline will be summarized in each period and percentage of subject with evaluations meeting criteria for pre-defined Potentially Clinically Significant values will be summarized in each period and across study periods by the upadacitinib doses. For selected laboratory parameters, a shift table analysis will be provided in each period and across study periods by the upadacitinib doses.

7.6 Sample Size Determination

Assuming:

- In SS1, 54% of subjects would be EASI 90 non-responders at Week 12.
- In SS2, 65% of the subjects would be EASI 90 responders at Week 12.
- There would be no more than 8% dropouts every 12 weeks.

A total sample size of 454 subjects will result in at least 96 subjects in SC1 and SC4, to ensure the half width of 95% CI will be within 10% for EASI 90 response estimation at Week 24.

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

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

For subjects in Japan only: This study will be conducted in Good Clinical Practice (GCP) compliance with Good Post-marketing Study Practice (GPSP).

8.3 Subject Confidentiality

For personal data that AbbVie controls and maintains, AbbVie has developed a robust security program to protect subject personal data focused on due diligence in design, managed change, and information security governance Information security policies govern the information security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's information security policies taking into account the sensitivity of the data.

Before data is shared with AbbVie, the study doctor and staff will replace any information that could directly identify a subject (such as name, address, and contact information) with a generic code which AbbVie cannot link to that subject's identity in order to protect the confidentiality of the data.

AbbVie has a Data Protection Impact Assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data-related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

AbbVie as the sponsor shall document any personal data breaches for which it is a controller and notify where required the competent national supervisory authority and/or affected participants and/or principal investigator and/or site personnel without undue delay and at the latest within 48 hours after becoming aware of such an incident. The sponsor shall create and maintain appropriate records of such an incident.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH GCP, and applicable local regulatory requirement(s), including EU Clinical Trial Regulation 536/2014. During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements, including EU Clinical Trial Regulation 536/2014.

11 START AND COMPLETION OF THE STUDY

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

The end-of-study is defined as the date of end of study participation by the last subject 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
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
ADL	activities of daily living
AE	Adverse event
AESIs	AE of special interest
Ag	antigen
ALC	Absolute lymphocyte count
ALT	alanine transaminase
ANC	Absolute neutrophil count
AO	As Observed
AST	aspartate transaminase
axSpA	axial spondyloarthritis
BCG	bacilli Calmette-Guérin
BSA	body surface area
CD	Crohn's disease
CI	confidence interval
COVID-19	Coronavirus Disease – 2019
CPK	creatine phosphokinase
CRP	C-reactive protein
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Treatment Evaluation Program
CXR	chest x-ray
CYP3A	cytochrome P450 3A
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DTP	direct-to-patient
DVT	deep vein thrombosis

EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
FSH	follicle-stimulating hormone
GCA	giant cell arteritis
GCP	Good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
GPSP	Good Post-marketing Study Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	HCV antibody
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
hsCRP	High-sensitivity C Reactive Protein
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
IGRA	Interferon-Gamma Release Assay
IL	interleukin
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent to Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
JAK	Janus kinase

JAK1	Janus kinase 1
JAK2	Janus kinase 2
MACE	major adverse cardiovascular event
MCID	minimum clinically important difference
MDA	minimal disease activity
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
N/A	not applicable
NCI	National Cancer Institute
NCS	Not clinically significant
NMSC	non-melanoma skin cancer
NRS	Numerical Rating Scale
OR	odds ratio
PCR	Polymerase chain reaction
PD	Premature discontinuation
PD Visit	Premature Discontinuation visit
PDE4	phosphodiesterase type 4
PGI	Patient Global Impression
PGIS	Patient Global Impression of Severity
PGIT	Patient Global Impression of Treatment
PK	Pharmacokinetic(s)
POEM	Patient Oriented Eczema Measure
PPD	purified protein derivative
PPE	Personal Protective Equipment
PRO	patient reported outcomes
PsA	psoriatic arthritis
PT	preferred term
PUVA	psoralen and ultraviolet A
QD	once daily
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid

ROA	Route of Administration
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC1	Study Cohort 1
SC2	Study Cohort 2
SC3	Study Cohort 3
SC4	Study Cohort 4
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SS1	Sub-Study 1
SS2	Sub-Study 2
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
TB	tuberculosis
TEAEs	treatment emergent adverse events
TNF	tumor necrosis factor
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UV	Ultra-violet
vIGA-AD	validated Investigator´s Global Assessment for AD
WBC	white blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-000: A Phase 3b/4 Randomized, Blinded, Treat-to-Target and Dose-Flexibility Study of Upadacitinib in Adult Subjects with Moderate to Severe Atopic Dermatitis (Flex-Up)

Protocol Date: 21 December 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 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 trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the trial.
        - Scientific value of the clinical trial, reliability, or robustness of data generated.
10. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Global Medical Affairs, Dermatology Global Medical Affairs Statistics

APPENDIX D. ACTIVITY SCHEDULE

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

Study Activities Table

Activity	Screening	Baseline	Week 4	Week 12	Week 16	Week 24	Unscheduled Visit	Premature Discontinuation Visit	30-day Follow Up Visit
	D-35 to D -1	D 1	D 29	D 85	D 113	D 169			
Visit Window (days)			± 3	± 3	± 3	± 3			± 3
Subject Information and Informed Consent	✓								
Eligibility criteria	✓	✓							
Medical/Surgical history	✓	✓							
Alcohol, nicotine and drug history	✓								
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB Risk Assessment Questionnaire	✓								
Patient Reported Outcomes: Worst Pruritus NRS (Handheld device)	✓	✓	✓	✓	✓	✓	✓	✓	
Patient Reported Outcomes: ADerm-SS, ADerm-IS (Baseline on site tablet device and then assessed daily via a handheld ePRO device through Week 24)		✓	✓	✓	✓	✓	✓	✓	
Patient Reported Outcomes:- DLQI, POEM, PGIS, PGIT		✓	✓	✓	✓	✓	✓	✓	
Subject hand-held device review (dispense at Screening)	✓	✓	✓	✓	✓	✓	✓	✓	
Body Weight	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	
Physical exam	✓	✓		✓		✓	✓	✓	
12-Lead ECG	✓								

Activity	Screening	Baseline	Week 4	Week 12	Week 16	Week 24	Unscheduled Visit	Premature Discontinuation Visit	30-day Follow Up Visit
	D-35 to D -1	D 1	D 29	D 85	D 113	D 169			
Visit Window (days)			± 3	± 3	± 3	± 3			± 3
Chest x-ray for TB Assessment	✓								
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigator Assessments (EASI, BSA, vIGA)	✓	✓	✓	✓	✓	✓	✓	✓	
For China sites only, dispense subject paper diary cards for AE symptoms, concomitant therapy, and investigational product administration as applicable	✓	✓	✓	✓	✓	✓			
For China sites only, review AE symptoms and concomitant therapy assessment from the subject paper diary cards		✓	✓	✓	✓	✓	✓	✓	✓
For China sites only, collect subject paper diary cards for AE symptoms, concomitant therapy, and investigational product administration		✓	✓	✓	✓	✓	✓	✓	✓
Serum pregnancy test (for all subjects of childbearing age)	✓								
Local urine pregnancy test (for all subjects of childbearing age)		✓	✓	✓	✓	✓	✓	✓	✓
Dispense urine pregnancy tests for monthly home testing			✓		✓				
Review and document pregnancy avoidance recommendations (for all subjects of childbearing age)		✓	✓	✓	✓	✓	✓	✓	
Beta-D-glucan (Japan only)	✓								
Central Laboratory Tests Clinical Chemistry, Hematology	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB Test (QuantiFERON-TB Gold Plus test [or interferon gamma release assay (IGRA) equivalent such as T-SPOT test] and/or local PPD skin test, if required)	✓								

Activity	Screening	Baseline	Week 4	Week 12	Week 16	Week 24	Unscheduled Visit	Premature Discontinuation Visit	30-day Follow Up Visit
	D-35 to D -1	D 1	D 29	D 85	D 113	D 169			
Visit Window (days)			± 3	± 3	± 3	± 3			± 3
Central Lab- HIV Screening, Hepatitis B and C Screening	✓								
Randomization/Drug assignment		✓		✓					
Dispense Study Drug		✓	✓	✓	✓				
Review and copy investigational product administration information from subject paper diary cards for China sites only			✓	✓	✓	✓	✓	✓	
Optional biomarker samples: Whole blood DNA		✓							
Optional biomarker samples: Plasma/serum proteomic		✓	✓	✓	✓	✓	✓	✓	
Optional biomarker samples: PBMC		✓	✓	✓					
Dispense wearable tool (Substudy Only)	✓								
Subject uses wearable tool for 7 nights prior to Baseline and following Visit (Substudy Only)		✓	✓	✓	✓				
Collect wearable tool (Substudy Only)						✓		✓	

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	08 April 2022
Version 2.0	01 February 2022
Administrative Change 1	05 April 2023

The purpose of this version is to update the protocol regarding EU Clinical Trial Regulation requirements, and to align the protocol with updated safety standards for upadacitinib study protocols.

The following changes were made for Version 3.0 of this protocol:

Protocol

- Applied administrative change and minor text edits as needed.
- Title page: Updated with EU CT number, updated Sponsor/Emergency Medical Contact information.
- Section 1 (Synopsis): Updated to align with version 3.0 revisions.
- Section 2.1 (Background and Rationale): Updated approvals for treatment with upadacitinib.
- Section 2.2 (Benefits and Risks to Subjects): Added AEs that have been observed in patients receiving JAK inhibitors including upadacitinib.
- Section 5.2 (Contraception Recommendations): Updated language for females of childbearing potential, added section on Contraceptive Counseling.
- Section 5.3 (Prohibited Medications and Therapy):
  - Updated list of prohibited biological therapies with immunosuppressive potential.
  - Updated examples of commonly used strong CYP3A inhibitors and inducers.
- Section 5.4 (Prior and Concomitant Therapy):
  - Added language to indicate that 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.
- Section 5.5 (Withdrawal of Subjects and Discontinuation of Study):
  - Updated language indicating that laboratory results or AEs that either meet the criteria for discontinuation of study drug, or rule out safe continuation of the study drug, would be determined by the investigator.
  - Updated malignancy language.
- Added Section 5.11, Publication Policy.
- Section 6.1 (Complaints and Adverse Events):

- Added Malignancy and Hypersensitivity Reactions and corresponding eCRFs.
- Added language for SUSAR reporting in the EU.
- Added Fractures and Retinal detachment to list of AESIs.

- Section 6.2 (Toxicity Management):
  - Updated language for management of serious infections, muscle-related symptoms, thrombosis events, and COVID-19.
  - Updated Elective and Emergency Surgeries to indicate that elective surgery prior to study primary endpoint must be discussed with the TA MD and performed with TA MD approval.
- Section 8.3 (Subject Confidentiality): Added language regarding the documentation of personal data breaches.
- Section 9 (Source Documents and Case Report Form Completion), Section 10 (Data Quality Assurance): Added Regulation [EU] No 536/2014.
- Appendix D (Activity Schedule):
  - To update the study activities table to allow for ADerm-SS and ADerm-IS PROs to be collected at the Baseline visit on the site tablet device).

Operations Manual

- Applied administrative changes and minor text edits as needed.
- Section 1 (Contacts): Updated Sponsor/Emergency Medical Contact information.
- Section 2.1 (Individual Treatment Period Visit Activities):
  - Added review and documentation of compliance with pregnancy avoidance recommendations for females of childbearing potential.
  - Updated Baseline visit with language for Post-Baseline Visits.
- Section 3.4 (Adverse Event Assessment): Updated to specify SAEs as protocol-related.
- Section 3.5 (Patient-Reported Outcomes):
  - Updated to indicate that The PRO instruments to be completed on the site device at scheduled study visits should be done before any interaction with site personnel has occurred (e.g., before drug administration, clinical assessments, and discussion of AEs or any review of laboratory findings) to avoid biasing the subject's response.
  - Updated to indicate that ADerm-SS and ADerm-IS will be administered on electronic handheld devices from **Baseline** through Week 24.
- Section 3.12 (Physical Examinations and Assessments): Updated CXR and Vaccine requirements.
- Section 3.14 (Clinical Laboratory Tests):
  - Updated to indicate that the investigator will record the laboratory result as an adverse event if the out-of-range value results in discontinuation of study drug, or necessitates therapeutic medical intervention.

- Added QuantiFERON-TB Gold Plus and Varicella antibody tests to Local Laboratory Tests.
- Indicated that results of any HIV antibody testing will be retained by the study site under confidential restrictions.
- Added language for Beta-D Glucan Testing (for Japan only).
- Updated TB testing procedures.
- Updated language for indeterminate QuantiFERON-TB Gold Plus test.

- Section 4.1 (Methods and Timing of Safety Assessment): Added supplemental eCRFs for Malignancy and Hypersensitivity Reactions.
- Section 4.2 (Reporting Adverse Events and Intercurrent Illnesses): updated SUSAR language to specify as in accordance with global and local requirements.