

abbvie ABT-494
M16-048 Protocol Amendment 5
EudraCT 2016-002451-21

1.0 Title Page

Clinical Study Protocol M16-048

A Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study to Evaluate ABT-494 (Upadacitinib) in Adult Subjects with Moderate to Severe Atopic Dermatitis

Incorporating Amendments 1, 2, 3, 3.01 (VHP Countries: Belgium, Finland, Germany, Ireland and Spain Only), 4 and 5

AbbVie Investigational Product: ABT-494 (upadacitinib)

Date: 30 August 2017

Development Phase: 2b

Study Design: This is a Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study

EudraCT Number: 2016-002451-21

Investigators: Multicenter Trial (Investigator information is on file at AbbVie)

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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	24 June 2016
Amendment 1	25 July 2016
Amendment 2	18 October 2016
Amendment 3	16 December 2016
Amendment 3.01	08 March 2017
Amendment 4	07 June 2017

The purpose of this amendment is to:

- Update Section 6.1.1.3, Adverse Events of Special Interest.
Rationale: Updated list of AEs of special interest to be consistent with the current AbbVie list of AEs of special interest.
- Update Section 8.1.6.2.1, Treatment-Emergent Adverse Events (TEAE).
Rationale: Updated list of AEs of special interest to be consistent with the current AbbVie list of AEs of special interest.

An itemized list of all changes made to this protocol under this amendment can be found in [Appendix Q](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M16-048
Name of Study Drug: ABT-494 (upadacitinib)	Phase of Development: 2b
Name of Active Ingredient: ABT-494 (upadacitinib)	Date of Protocol Synopsis: 30 August 2017
Protocol Title: A Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study to Evaluate ABT-494 (Upadacitinib) in Adult Subjects with Moderate to Severe Atopic Dermatitis	
Objective: To evaluate the safety and efficacy of multiple doses of ABT-494 (upadacitinib) monotherapy versus placebo in the treatment of adults with moderate to severe atopic dermatitis.	
Investigators: Multicenter	
Study Sites: Approximately 45	
Study Population: Adult female and male subjects who are ≥ 18 and ≤ 75 years of age with moderate to severe atopic dermatitis defined by a baseline Eczema Area and Severity Index (EASI) of ≥ 16 , affected Body Surface Area (BSA) of $\geq 10\%$ and Investigator's Global Assessment (IGA) of ≥ 3 .	
Number of Subjects to be Enrolled: Approximately 160 subjects (40 subjects per treatment group)	
Methodology: This is an 88-week Phase 2b, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the safety and efficacy of ABT-494 (upadacitinib) in adult subjects with moderate to severe atopic dermatitis. In Period 1, subjects will be randomized in a 1:1:1:1 ratio to one of four treatment groups: (1) ABT-494 7.5 mg, (2) ABT-494 15 mg, (3) ABT-494 30 mg, (4) matching placebo, once daily for 16 weeks. The primary endpoint analysis will be performed at Week 16. Randomization will be stratified by geographic region (US/PR/Canada, EU/AUS, and Japan). Enrollment in Japan will be capped at 10% of subjects (4 subjects per group). Group 1: ABT-494 7.5 mg QD for 16 weeks Group 2: ABT-494 15 mg QD for 16 weeks Group 3: ABT-494 30 mg QD for 16 weeks Group 4: Matching Placebo for 16 weeks The analysis of the double-blind 16-week period of the study (Period 1), including the primary endpoint analysis, will be conducted after all subjects have either completed the Period 1 or discontinued from the study; and the data regarding Period 1 have been cleaned and an interim database lock is performed. This efficacy analysis is the only and final analysis of the double-blind Period 1, thus no adjustment of alpha-level is needed. In addition, there will be an interim analysis after all subjects have either reached Week 32 or discontinued from the study; and the data is cleaned. In Period 1, discontinuation from study drug will be mandatory for any subject with an EASI score worsening of 25% or more compared with their Baseline EASI score at any 2 consecutive scheduled study visits from Week 4 to Week 12.	

Methodology (Continued):

Subjects who complete Period 1 will be re-randomized at Week 16 within their original treatment group assignments to either ABT-494 (upadacitinib) or placebo into a 72-week double-blind, placebo controlled treatment period (Period 2) in a 1:1 ratio as shown in Figure 1 (study design). Randomization will be stratified by geographic region and EASI 75 response at Week 16. At the Week 16 visit, all subjects will be re-randomized as follows into Period 2:

- Subjects from Group 1 in Period 1: ABT-494 7.5 mg QD or matching placebo for 24 weeks
- Subjects from Group 2 in Period 1: ABT-494 15 mg QD or matching placebo for 24 weeks
- Subjects from Group 3 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks
- Subjects from Group 4 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks

For subjects re-randomized to placebo, ABT-494 7.5 mg QD or ABT-494 15 mg QD in Period 2, blinded rescue therapy with ABT-494 30 mg QD will be provided after the first instance of a < EASI 50 response starting at the Week 20 visit (4 weeks after re-randomization into Period 2). These subjects will continue on ABT-494 30 mg QD for the remainder of the study. These subjects will continue on ABT-494 30 mg QD for the remainder of the study.

During Period 2, concomitant class III – IV, medium potency topical corticosteroid treatment will be permitted at the Week 24 visit and thereafter in subjects after a second instance of < EASI 50 response in any two Period 2 study visits beginning from Week 20 (see Section 5.2.3.4 for a list of permitted treatments). For subjects who receive topical corticosteroid rescue therapy, an additional visit will be required 4 weeks later. Discontinuation from study drug will be mandatory for subjects with < EASI 50 response compared with their Baseline EASI score 4 weeks following rescue with topical corticosteroids or at any visit thereafter.

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

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult male or female, ≥ 18 and ≤ 75 years old at Screening.
2. Atopic dermatitis with a diagnosis confirmed by a dermatologist (according to the Hanifin and Rajka criteria); and also onset of symptoms at least 1 year prior to baseline.
3. Moderate to severe atopic dermatitis defined by an EASI ≥ 16 , BSA $\geq 10\%$ and an IGA score ≥ 3 at the Baseline visit.
4. Documented history (within 1 year prior to the screening visit) of inadequate response to treatment with topical corticosteroids (TCS), or topical calcineurin inhibitors (TCI), or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
5. Twice daily use of an additive-free, bland emollient for at least 7 days prior to Baseline.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

1. Prior exposure to any systemic or topical JAK inhibitor (including but not limited to tofacitinib, baricitinib, ruxolitinib, and filgotinib).
2. Treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin within 10 days prior to the Baseline visit.
3. Prior exposure to dupilumab.
4. Prior exposure to any investigational systemic treatment within 30 days or 5 half-lives (whichever is longer) of the Baseline visit or is currently enrolled in another clinical study.
5. Treatment with omalizumab within 3 months prior to the Baseline visit.
6. Prior exposure to systemic therapy for atopic dermatitis, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors and mycophenolate mofetil within 4 weeks prior to the Baseline visit.
7. Subject with other active skin diseases or skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline visit or would interfere with the appropriate assessment of atopic dermatitis lesions.
8. Phototherapy treatment, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks prior to the Baseline visit and during the study.

Investigational Product: ABT-494 (upadacitinib)

Doses:
 ABT-494 7.5 mg QD
 ABT-494 15 mg QD
 ABT-494 30 mg QD

Mode of Administration: Oral

Reference Therapy: Matching placebo

Dose: N/A

Mode of Administration: Oral

Duration of Treatment: 88 weeks

Criteria for Evaluation:

Efficacy:

Primary Endpoint:

Mean percent (%) change from Baseline (Day 1) in EASI score at Week 16.

Secondary Endpoints:

- Proportion of subjects achieving an EASI 75 response, defined as at least a 75% reduction in EASI score, at Week 16 relative to the Baseline (Day 1)
- Proportion of subjects achieving an Investigator Global Assessment (IGA) of 0 or 1 at Week 16
- Percent change from Baseline to Weeks 2, 8 and 16 in pruritus numerical rating scale (NRS)
- Percent change in EASI score from Baseline at Week 8
- Percent change in SCORAD score from Baseline at Weeks 8 and 16

Criteria for Evaluation (Continued):

Efficacy (Continued):

Secondary Endpoints:

- Proportion of subjects achieving EASI 50/75/90 response at Weeks 8 and 16
- Proportion of subjects achieving SCORAD 50/75/90 response at Weeks 8 and 16
- Proportion of subjects with Dermatology Life Quality Index (DLQI) = "0" or "1" at Weeks 8 and 16
- Change from Baseline in DLQI at Weeks 8 and 16
- Change and percent change from Week 16 (re-randomization) in EASI score at all Period 2 visits
- Time to loss of EASI 50 response relative to Baseline among those who were re-randomized as EASI 75 responders at Week 16
- Summary of EASI 75 at all visits in Period 2 among those who were re-randomized as EASI 75 non-responders at Week 16

Exploratory Endpoints:

- Time to EASI 50/75/90 and IGA "0" or "1" response in Period 1
- Proportion of subjects achieving EASI 50/75/90/100 response at all visits
- Proportion of subjects achieving SCORAD 50/75/90 response at all visits
- Change from Baseline to Week 16 in Patient Oriented Eczema Measure (POEM)
- Change from Baseline to Week 16 in Medical Outcomes Study (MOS) Sleep Scale
- Change from Baseline to Week 16 in Asthma Symptoms Questionnaire
- Change from Baseline to Week 16 in Daytime Nasal Symptom Questionnaire
- Change from Baseline in total sleep time per night (TST min), Sleep Efficiency (%), Wake After Sleep Onset (WASO), number of scratching events per hour, mean activity during rest (sleep) periods as measured by actigraphy.

Primary and secondary variables will also be evaluated at all scheduled visits through Week 88.

Exploratory Research Variables and Validation Studies (Optional):

Prognostic, predictive, surrogate and pharmacodynamics biomarkers signatures may be evaluated. To this end, blood and skin biopsies samples will be collected at various time points. Assessments will include but may not be limited to nucleic acids, proteins, metabolites, or lipids.

Selected sites will be asked to perform a complete investigation of biomarkers. For such sites, these assessments (blood samples and skin biopsy collections) will be made mandatory as part of the main study. There will be a specific Informed Consent Form (ICF) for subjects in these selected sites.

Pharmacokinetic:

Blood samples for assay of ABT-494 (upadacitinib) will be collected at each visit beginning at Week 2. Blood samples at Week 2 and 4 visits will be collected prior to dosing if possible. For all other visits, blood samples will be collected at any time during the visit.

Safety:

Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiogram, and clinical laboratory testing (hematology, chemistry, and urinalysis).

Statistical Methods:

Efficacy:

Efficacy analyses will be carried out in the Intent-to-treat population, which includes all randomized subjects. All statistical tests will be conducted at two-sided alpha level of 0.05 unless otherwise specified. Pairwise comparison of each ABT-494 (upadacitinib) treatment group versus placebo will be performed.

Categorical variables will be analyzed using the Cochran-Mantel-Haenszel test adjusting for stratification factors.

Continuous variables will be analyzed using the analysis of covariance (ANCOVA) model with treatment group and stratification factors as fixed effects, and the corresponding baseline value as covariates.

Time to event variables will be analyzed using Kaplan-Meier methodology.

Multiple imputation and last observation carried forward (LOCF), and as-observed approaches will be utilized for continuous endpoints. Non-responder Imputation will be the primary approach to impute missing values for the categorical endpoints.

A total of 160 subjects will be randomized to three treatment groups and placebo in a ratio of 1:1:1:1. The sample size for this study is based on the percent change in EASI from baseline at Week 16. Assuming a percent change in EASI from baseline at Week 16 of 35, 45, 60, and 70 in the placebo, 7.5 mg, 15 mg, and 30 mg arms with a standard deviation of 40 and a maximum efficacy of 80, a sample size of 40 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest (e.g., the minimum effective dose, MED) using MCP-Mod (Multiple comparison procedure and modeling) approach. This approach provides 99% average power to detect a dose effect at 5% level of significance (one-sided) with the linear, E_{max} , exponential, logistic and $sigE_{max}$ models pre-specified as likely candidates to characterize the dose-response for ABT-494 for the percent change in EASI.

A sample of size 40 per group provides 97% power to detect a significant difference between 30 mg QD and placebo, and 78% power to detect a significant difference between 15 mg QD and placebo at two-sided level of significance of 5.0%.

Pharmacokinetic:

A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values for ABT-494 (upadacitinib) oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

Safety:

Safety analyses will be carried out using the safety population, for both periods, which includes all subjects who receive at least one dose of study medication and is based on treatments actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital sign results. Frequency tables and lists of subjects with treatment-emergent AEs (TEAEs) by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term will be presented. AEs will further be analyzed by severity and relationship to study drug as assessed by the investigator. Summaries will include percentage of patients and events per 100 patient-years. The changes from baseline in vital signs and clinical laboratory values will be analyzed in a descriptive manner.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
AD	Atopic Dermatitis
ADerm-IS	Atopic Dermatitis Impact Scale
ADerm-SS	Atopic Dermatitis Symptom Scale
ADL	Activities of Daily Living
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ANT	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BCG	Bacille Calmette- Guerin
bHCG	Beta Human Chorionic Gonadotropin
BL	Baseline Visit
BSA	Body Surface Area
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CCP	Cyclic Citrullinated Peptide
CPK	Creatine Phosphokinase
CYP3A	Cytochrome P450 3A
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-Ray
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DO	Doctor of Osteopathy
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EDC	Electronic Data Capture
ePRO	Electronic Patient Recorded Outcome
FDA	US Food and Drug Administration

F/U	Follow-up
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GFR	Estimated Glomerular Filtration Rate
HBV	Hepatitis B
HBsAg	Hepatitis B Surface Antigen
HBsAb	Hepatitis B Surface Antibody
HCV	Hepatitis C
HCV Ab	Hepatitis C virus antibody
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HsCRP	High Sensitive C Reactive Protein
ICH	International Conference on Harmonization
DMC	Data Monitoring Committee
IEC	Independent Ethics Committee
IGA	Investigators Global Assessment
IGRA	Interferon-Gamma Released Assay
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
JAK	Janus Activated Kinase
LDL-C	Low-Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
MDRD	Modification of diet in renal disease
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
MOS	Medical Outcomes Study
NCI	National Cancer Institute
NK	Natural Killer
NKT	Natural Killer T
NMSC	Non-Melanoma Skin Cancer
NRS	Numerical Rating Scale

NYHA	New York Heart Association
PA	Physician Assistant
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Premature Discontinuation
PDE4	Phosphodiesterase Type 4
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPD	Purified Protein Derivate
PRO	Patient Reported Outcome
PUVA	Photochemotherapy
QD	Once Daily
QTc	QT interval corrected for heart rate
QTcF	Friedericia's correction formula
RAVE	EDC System from Medidata
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TB	Tuberculosis
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
ULN	Upper Limit of Normal
UVA	Ultraviolet A
UVB	Ultraviolet B
WBC	White Blood Count
Wk	Week

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3.0 Introduction

Atopic Dermatitis

Atopic Dermatitis (AD; also known as atopic eczema) is an inflammatory, pruritic, chronic or chronically relapsing skin disease. Common clinical characteristics include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification, but these vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families.¹ Sleep disturbance is commonly associated with AD and stems in large part from the significant itch associated with the disease.^{2,3}

AD is also associated with multiple other comorbid conditions, including a higher prevalence of other atopic diseases such as rhinitis, food allergies and asthma with the severity of eczema directly related to the severity of these comorbidities.⁴

The diagnosis of AD is made clinically and is based on historical features, morphology and distribution of skin lesions, and associated clinical signs. Several criteria have been developed by various groups to aid in classification. One of the earliest and most recognized sets of diagnostic criteria is the 1980 Hanifin and Rajka criteria⁵ which require that 3 of 4 major criteria and 3 of 23 minor criteria be met.

AD is one of the most common skin diseases which affects up to 20% of children and 1 – 3% of adults worldwide.⁶ In approximately 70% of cases, the onset of AD starts in children under 5 years of age⁷ and while the majority of affected individuals have resolution of disease by adulthood, it persists in about 10% to 30% of cases.⁸ In addition, a smaller percentage of patients first develop symptoms of AD as adults.⁹

JAK Inhibition

Evidence suggests that inhibition of Janus kinase (JAK)-mediated pathways may be a promising approach for the treatment of patients with moderate to severe AD.¹⁰ AbbVie

is developing a small molecule inhibitor of JAK, ABT-494 (upadacitinib), that may address the current needs.

The JAK family is composed of 4 family members: JAK1, 2, 3, and Tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors such as common gamma-chain receptors and the glycoprotein 130 transmembrane proteins.¹¹ Activation of JAK pathways 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.

Hence, the JAK family has evoked considerable interest in the area of inflammatory diseases leading to the development of JAK inhibitors with different selectivity profiles against JAK1, JAK2, JAK3, and Tyk2, of which tofacitinib has showed initial indication of efficacy in individuals with AD.^{12,13} Although tofacitinib, a non-selective JAK inhibitor, has demonstrated efficacy in both rheumatoid arthritis and plaque psoriasis, questions regarding the safety profile remain for both indications, including serious infections, herpes zoster reactivation, malignancies, and hematologic adverse events (AEs).

The second generation of JAK inhibitors, with different selectivity profiles against JAK1, JAK2, JAK3, and Tyk2, are in development.¹⁴ ABT-494 (upadacitinib) is a novel selective JAK1 inhibitor currently being developed for RA, UC and CD. In an in vitro setting, ABT-494 potently inhibits JAK1 activity, but to a lesser degree, inhibits the other isoforms, JAK2 and JAK3. The enhanced selectivity of ABT-494 against JAK1 may offer an improved benefit-risk profile in patients with moderate to severe AD.

The clinical hypothesis is that ABT-494 (upadacitinib) should be effective in targeting Th2-mediated inflammation and itch associated with AD by interfering with JAK1-mediated signaling pathways that are central to its pathophysiology (TSLP, IL31, IL-4 and IL13 all signal through JAK1)^{15,16} without causing excessive anemia due to its reduced activity against JAK2, which is essential for erythropoietin signaling. ABT-494

is also less potent against JAK3, an important component of lymphocyte activation and function. As such, treatment with ABT-494, a selective JAK1 inhibitor with reduced JAK3 inhibition, could result in a decreased risk for infection (including viral reactivation) and/or malignancy compared to a pan JAK inhibitor or less selective JAK inhibitors.

ABT-494 Pharmacokinetics

After administration of ABT-494 (upadacitinib) once-daily tablet formulation, ABT-494 maximum plasma concentration was achieved within 2 to 4 hours and its terminal elimination half-life was 9 to 14 hours. ABT-494 displayed no significant accumulation in plasma with multiple dosing. Food has no clinically meaningful effect on ABT-494 exposure from the once-daily formulation; therefore, ABT-494 can be administered without regard to meals.

In vitro studies suggest that ABT-494 is not an inhibitor of cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 at concentrations exceeding those relevant clinically. ABT-494 increased mRNA expression for CYP3A4 and CYP2B6 in vitro in a concentration-dependent manner. However, physiologically-based pharmacokinetic modeling suggests that ABT-494 does not affect plasma concentrations of concomitant medications that are substrates for CYP3A or CYP2B6 at the relevant clinical doses.

3.1 Differences Statement

This Phase 2 study differs from other ABT-494 (upadacitinib) studies as it is the first to evaluate the safety and efficacy of multiple dosages of ABT-494 versus placebo in the treatment of moderate to severe AD.

3.2 Benefits and Risks

Treatment of AD in adult patients depends on the extent and severity of disease. Topical agents alone are commonly used for mild to moderate cases. The most commonly used topical agents are corticosteroids, calcineurin inhibitor agents and moisturizers. When

topical therapies are insufficient for treating the signs and symptoms of AD, systemic therapy or phototherapy are generally added to topical agents.¹⁷

Treatment guidelines developed by the American Academy of Dermatology recommend the use of systemic immunomodulatory agents for patients in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease. These guidelines recognize that insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication.¹⁸ Importantly, in addition to the lack of well-controlled efficacy data supporting their use in moderate to severe AD, the duration of use of many traditional systemic immunomodulatory agents are limited due to cumulative toxicity. This significant unmet need has also been independently detected by a recent systematic review of systemic treatments for moderate to severe AD that concluded that, although 12 different interventions for moderate to severe AD have been studied in 34 RCTs, strong recommendations are only possible for the short-term use of cyclosporin A.¹⁹

At this time there is no FDA-approved systemic treatment and only one EMA-approved systemic treatment (cyclosporin A) for AD. Thus, there is a high unmet need for a significant number of patients with an inadequate response to topical agents.

ABT-494 (upadacitinib) is a novel selective orally available JAK1 inhibitor with the potential to decrease Th2-mediated skin inflammation and itch mediated by JAK1 signaling in AD, while having minimal inhibitory effects on JAK2 and JAK3. This could potentially minimize some of the reported safety concerns with non-selective JAK inhibition which are thought to be mediated by inhibition of JAK2 and JAK3 signaling pathways.

4.0 Study Objective

To evaluate the safety and efficacy of multiple doses of ABT-494 (upadacitinib) monotherapy versus placebo in the treatment of adults with moderate to severe AD.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is an 88-week Phase 2b, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the safety and efficacy of ABT-494 (upadacitinib) in adult subjects with moderate to severe AD.

The study was designed to enroll approximately 160 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

The duration of the study will be up to 88 weeks and will include a 35-day maximum screening period, a 16-week double-blind treatment period (Period 1) and a 72-week double-blind treatment period (Period 2). In addition, a 30-day follow-up visit (or phone call if a visit is not possible) should occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

In Period 1, subjects will be randomized in a 1:1:1:1 ratio to one of four treatment groups: (1) ABT-494 7.5 mg, (2) ABT-494 15 mg, (3) ABT-494 30 mg, (4) matching placebo, once daily for 16 weeks. The primary endpoint analysis will be performed at Week 16. Randomization will be stratified by geographic region (US/PR/Canada, EU/AUS, and Japan). Enrollment in Japan will be capped at 10% of subjects (approximately 4 subjects per group).

Group 1: ABT-494 7.5 mg QD for 16 weeks

Group 2: ABT-494 15 mg QD for 16 weeks

Group 3: ABT-494 30 mg QD for 16 weeks

Group 4: Matching Placebo for 16 weeks

The analysis of the double-blind 16-week period of the study (Period 1), including the primary endpoint analysis, will be conducted after all subjects have either completed the

Period 1 or discontinued from the study; and the data regarding Period 1 have been cleaned and an interim database lock is performed. This efficacy analysis is the only and final analysis of the double-blind period, thus no adjustment of alpha-level is needed. In addition, there will be an interim analysis after all subjects have either reached Week 32 or discontinued from the study; and the data is cleaned.

In Period 1, discontinuation from study drug will be mandatory for any subject with an EASI score worsening of 25% or more compared with their Baseline EASI score at any 2 consecutive scheduled study visits from Week 4 to Week 12.

Subjects who complete Period 1 will be re-randomized at Week 16 within their original treatment group assignment to either ABT-494 (upadacitinib) or placebo into a 72-week double-blind, placebo controlled treatment period (Period 2) in a 1:1 ratio as shown in [Figure 1](#) (study design). Randomization will be stratified by geographic region and EASI 75 response at Week 16. At the Week 16 visit, all subjects will be re-randomized as follows into Period 2:

- Subjects from Group 1 in Period 1: ABT-494 7.5 mg QD or matching placebo for 24 weeks
- Subjects from Group 2 in Period 1: ABT-494 15 mg QD or matching placebo for 24 weeks
- Subjects from Group 3 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks
- Subjects from Group 4 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks

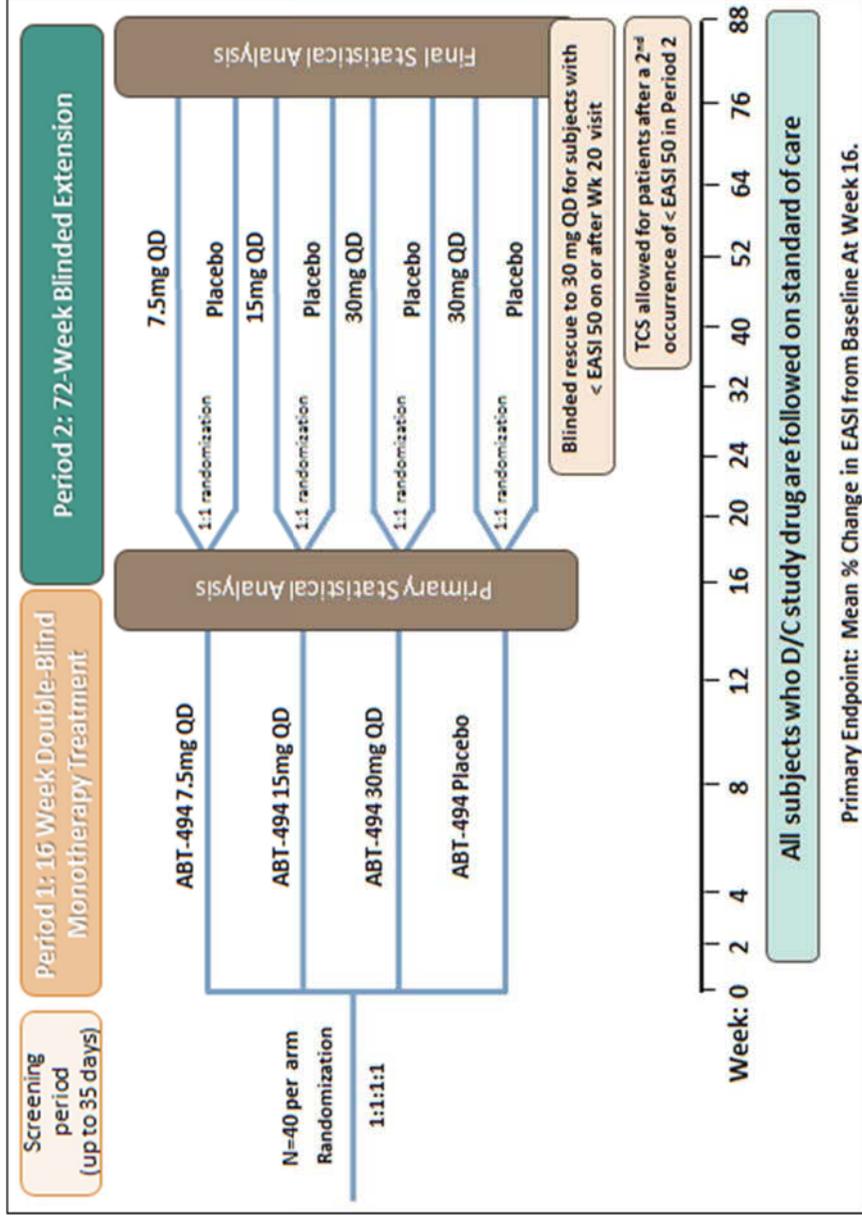
For subjects re-randomized to placebo, ABT-494 7.5 mg QD or ABT-494 15 mg QD in Period 2, blinded rescue therapy with ABT-494 30 mg QD will be provided after the first instance of a < EASI 50 response starting at the Week 20 visit (4 weeks after re-randomization into Period 2). These subjects will continue on ABT-494 30 mg QD for the remainder of the study.

During Period 2, concomitant class III – IV, medium potency topical corticosteroid treatment will be permitted at the Week 24 visit and thereafter in subjects after a second instance of < EASI 50 response in any two Period 2 study visits beginning from Week 20 (see Section 5.2.3.4 for permitted treatments). For subjects who receive topical corticosteroid rescue therapy, an additional visit will be required 4 weeks later. Discontinuation from study drug will be mandatory for subjects with < EASI 50 response compared with their Baseline EASI score 4 weeks following rescue with topical corticosteroids or at any visit thereafter.

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

A schematic of the overall study design is shown in [Figure 1](#).

Figure 1. Study Design



Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in [Table 2](#). Lab values can be re-tested once during the screening period.

Beginning at the Screening Visit, twice daily use of an additive-free, bland emollient is required for at least 7 days prior to Baseline and during the study.

Subjects that initially screen fail for the study are permitted to re-screen once following re-consent. For additional re-screening, AbbVie Therapeutic Area Medical/Scientific Director approval is required. These cases must be brought to the attention of the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director as needed and provide a recommendation.

All screening procedures with the possible exceptions noted below will be repeated during re-screening. The subject must meet all the inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) or a purified protein derivative (PPD) test (or equivalent), or chest x-ray and electrocardiogram (ECG), these tests will not be required to be repeated for re-screening provided the conditions noted in [Section 5.2](#) are met and no more than 90 days have passed.

Period 1: 16-Week Treatment Period

Period 1 will begin at the Baseline Visit (Day 1) and will end at the Week 16 Visit. At the Baseline Visit, subjects who meet all the inclusion criteria and none of the exclusion criteria described in [Section 5.2.1](#) and [Section 5.2.2](#) will be enrolled into the study and randomized to double-blind treatment. During Period 1 of the study, subjects will visit

the study site at Baseline, Weeks 2, 4, 8, 12, and 16. A \pm 3 day window is permitted around scheduled study visits. Subjects will start on their respective dose at Baseline.

Twice daily use of an additive-free, bland emollient is required throughout Period 1.

Period 2: 72-Week Treatment Period

Period 2 will begin after the Week 16 Visit and will end at the Week 88 Visit. At the Week 16 Visit, subjects will be re-randomized as described in Section 5.1. During Period 2 of the study, subjects will visit the study site at Weeks 20, 24, 32, 40, 52, 64, 76, and 88. A \pm 5 day window is permitted around scheduled study visits. Subjects will start on their assigned treatment at the Week 16 visit.

The last dose of study drug is taken the day prior to the Week 88 visit.

Twice daily use of an additive-free, bland emollient is required throughout Period 2.

Discontinuation of Study Drug and Continuation of Study Participation

Subjects may discontinue study drug treatment, but may choose to continue to participate in the study (refer to Section 5.4.1 for additional details). Subjects who prematurely discontinue study drug should complete a Premature Discontinuation Visit (PD visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Table 2 and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood and skin biopsy sample collection for optional exploratory research and validation studies. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply.

In Period 1, discontinuation from study drug will be mandatory for any subject with an EASI score worsening of 25% or more compared with their Baseline EASI score at any 2 consecutive scheduled study visits from Week 4 to Week 12.

In Period 2, discontinuation from study drug will be mandatory for subjects with < EASI 50 response compared with their Baseline EASI score 4 weeks following rescue with topical corticosteroids or at any visit thereafter.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time (refer to Section 5.4.2 for additional details). 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 of study drug discontinuation. In addition, if the subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Follow-Up Period

Subjects who prematurely discontinue the study or complete the study will have a follow-up visit (or phone call if a visit is not possible) approximately 30 days after the last administration of study drug to obtain information on any new or ongoing AEs, and to collect vital signs and clinical laboratory tests.

5.2 Selection of Study Population

It is anticipated that approximately 160 adult subjects with moderate to severe atopic dermatitis will be randomized at approximately 45 study centers globally.

A subject may be enrolled in this study provided that he/she has met all of the inclusion criteria and none of the exclusion criteria specified in this protocol.

5.2.1 Inclusion Criteria

1. Adult male or female, ≥ 18 and ≤ 75 years old at Screening.

2. Atopic dermatitis with a diagnosis confirmed by a dermatologist (according to the Hanifin and Rajka criteria); and also onset of symptoms at least 1 year prior to baseline.
3. Moderate to severe AD defined by an EASI \geq 16, BSA \geq 10% and an IGA score \geq 3 at the Baseline visit.
4. Documented history (within 1 year prior to the screening visit) of inadequate response to treatment with topical corticosteroids (TCS), or topical calcineurin inhibitors (TCI), or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
5. Twice daily use of an additive-free, bland emollient for at least 7 days prior to Baseline.
6. A negative serum pregnancy test for all female subjects at the Screening Visit and a negative urine pregnancy test for all female subjects of childbearing potential at the Baseline Visit prior to administration of first dose of study drug. Note: subjects with borderline pregnancy test at Screening must have a serum pregnancy test \geq 3 days later to document continued lack of a positive result.
7. If female, subject must be postmenopausal OR permanently surgically sterile OR for Women of Childbearing Potential practicing at least one protocol specified method of birth control (Section 5.2.4), that is effective from the Baseline visit through at least 30 days after the last dose of study drug.

If male and subject is sexually active with a female partner(s) of childbearing potential, he must practice the protocol specified contraception from the Baseline visit through at least 30 days after last dose of study drug (Section 5.2.4).

Additional local requirements may apply. Refer to [Appendix P](#) for local requirements in Canada.

8. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. For subjects in Japan

only: if a subject is under 20 years of age, then the subject and their parent or legal guardian must voluntarily sign and date an informed consent.

Rationale for Inclusion Criteria

- | | |
|-------|--|
| 1 – 5 | To select the appropriate subject population |
| 6 – 7 | The impact of ABT-494 on pregnancy and reproduction is unknown |
| 8 | In accordance with harmonized Good Clinical Practice (GCP) |

5.2.2 Exclusion Criteria

1. Prior exposure to any systemic or topical JAK inhibitor (including but not limited to tofacitinib, baricitinib, ruxolitinib, and filgotinib).
2. Treatment with topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin within 10 days prior to the Baseline visit.
3. Prior exposure to dupilumab.
4. Prior exposure to any investigational systemic treatment within 30 days or 5 half-lives (whichever is longer) of the Baseline visit or is currently enrolled in another clinical study.
5. Treatment with omalizumab within 3 months prior to the Baseline visit.
6. Prior exposure to systemic therapy for AD, including but not limited to corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors and mycophenolate mofetil within 4 weeks prior to the Baseline visit.
7. Use of traditional Chinese medicine within 4 weeks prior to the Baseline visit.
8. Subject with other active skin diseases or skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline visit or would interfere with the appropriate assessment of AD lesions.

9. Phototherapy treatment, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks prior to the Baseline visit and during the study.
10. Current or past history of infection including:
 - History of recurrent or disseminated (even a single episode) herpes zoster;
 - History of disseminated (even a single episode) herpes simplex;
 - History of known invasive infection (e.g., listeriosis and histoplasmosis);
 - Known immunodeficiency syndrome;
 - Subject has active TB or meets TB exclusionary parameters (refer to Section 5.3.1.1 for specific requirements for TB testing);
 - Non-skin related active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the Baseline Visit.
 - Chronic recurring infection and/or active invasive infection (e.g., listeriosis and histoplasmosis) and viral infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study;
 - Active HBV, HCV, or HIV defined as:
 - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects (and for Hepatitis B surface antibody positive [+] subjects in Japan only);
 - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
 - HIV: confirmed positive anti-HIV antibody (HIV Ab) test.
11. Underlying medical diseases or problems including but not limited to the following:
 - Clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Friedericia's correction formula (QTcF) > 500 msec.;

- History of moderate to severe congestive heart failure (New York Heart Association class III or IV), recent (within past 6 months) cerebrovascular accident, myocardial infarction, or coronary stenting, or uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg;
 - Subject has been a previous recipient of an organ transplant;
 - History of gastrointestinal perforation, diverticulitis or significantly increased risk for GI perforation per investigator judgment;
 - Conditions that could interfere with drug absorption including but not limited to short bowel syndrome;
 - History of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix;
 - History of clinically significant medical conditions or any other reason which in the opinion of the investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the protocol; or permanently wheelchair-bound or bedridden or very poor functional status which prevents the ability to perform self-care.
12. Systemic use of known strong cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers from Screening through the end of the study (refer to [Table 1](#) for examples of commonly used strong CYP3A inhibitors and inducers).
 13. Receipt of any live vaccine within 4 weeks (8 weeks in Japan) prior to the Baseline Visit, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.
 14. History of an allergic reaction or significant sensitivity to constituents of the study drugs and/or other products in the same class.
 15. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months preceding the Baseline Visit.
 16. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.

17. Male subject who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of study drug.
18. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug (Baseline Visit):
 - Serum aspartate transaminase (AST) $> 2 \times$ ULN;
 - Serum alanine transaminase (ALT) $> 2 \times$ ULN;
 - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m²;
 - Total white blood cell count (WBC) $< 2,500/\mu\text{L}$;
 - Absolute neutrophil count (ANC) $< 1,500/\mu\text{L}$;
 - Platelet count $< 100,000/\mu\text{L}$;
 - Absolute lymphocyte count $< 800/\mu\text{L}$;
 - Hemoglobin < 10 g/dL.
19. Consideration by the Investigator, for any reason, that the subject is an unsuitable candidate to receive ABT-494 (upadacitinib) or participate in this study.
20. For subjects in Japan only: Positive result of beta-D-glucan (screening for pneumocystis jiroveci infection).

Rationale for Exclusion Criteria

1 – 7, 9	To select the appropriate subject population
8, 10 – 15, 18 – 20	To ensure safety of the subjects throughout the study
16, 17	ABT-494 is teratogenic in both rats and rabbits. The impact of ABT-494 on pregnancies is unknown

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements including folic acid) that the subject is receiving

within 28 days prior to Screening, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route, and frequency on the appropriate electronic case report form (eCRF).

Vaccines recommended by local guidelines should be considered. If the investigator chooses to administer a vaccine, this should be completed before first dose of study drug with appropriate precautions and time interval. It is recommended that subjects be up to date for recommended vaccines that are inactivated, toxoid or biosynthetic vaccines, such as injectable flu vaccine, pneumococcal, and pertussis (Tdap). It is recommended that the live herpes zoster vaccine be considered for administration at least 4 weeks (8 weeks in Japan) before the first dose of study drug in subjects greater than 50 years of age (per label). If the herpes zoster vaccine is to be administered pre-existing immunity should be confirmed antibody testing at or prior to screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative the herpes zoster vaccine should not be administered. See Section 5.2.3.3 for a list of commonly used live vaccines.

If there are any questions regarding concomitant or prior therapies the AbbVie Therapeutic Area Scientific Director should be contacted who will then discuss with the AbbVie Medical Director and provide a recommendation.

5.2.3.1 Prior Therapy

Any systemic treatments for AD since initial diagnosis (as determined through medical history records or through subject or parent or legal representative interview) and any prescribed treatments for AD prior to study entry will be recorded on the eCRF. For subjects previously treated with systemic agents, the duration of therapy, maximum dose, and reason(s) for termination of treatment with should be documented.

5.2.3.2 Permitted Background and Concomitant Therapy

Beginning at the Screening Visit, twice daily use of an additive-free, bland emollient is required for at least 7 days prior to Baseline and during the study.

Oral antibiotics for up to 2 weeks for AD-associated superficial skin infections are allowed and will be captured as concomitant therapy.

5.2.3.3 Prohibited Therapy

Non-Biologic Systemic Therapies

JAK Inhibitors

Prior and concomitant oral and topical exposure to any other JAK inhibitors besides the investigational drug, ABT-494 (including but not limited to ruxolitinib, tofacitinib, baricitinib, and filgotinib) is not allowed.

Other Non-Biologic Systemic Therapy

Systemic therapy for the treatment of AD is not allowed during the study, including but not limited to:

- methotrexate,
- cyclosporine,
- azathioprine,
- PDE4-Inhibitors,
- mycophenolate mofetil.

Corticosteroids

Oral, parenteral, and intralesional corticosteroids are NOT allowed during the study.

Biologic Therapies

All prior and concomitant targeted biologic therapies are prohibited during the study. Examples of targeted biologic therapies include but are not limited to the following:

- Zolair (omalizumab);
- Dupilumab;
- Adalimumab;
- Etanercept;
- Infliximab;
- Abatacept;
- Anakinra;
- Rituximab;
- Natalizumab;
- Efalizumab;
- Tocilizumab;
- Golimumab;
- Certolizumab;
- Ustekinumab;
- Belimumab;
- Secukinumab;
- Denosumab

Phototherapy, Tanning Booth, and Extended Sun Exposure

UVB or UVA phototherapy including PUVA for at least 4 weeks prior to the Baseline visit and during the study.

Tanning booth use or extended sun exposure that could affect disease severity or interfere with disease assessments for at least 4 weeks prior to the Baseline visit and during the study.

Topical Therapy

No topical treatments for AD, including but not limited to calcineurin inhibitors, corticosteroids, prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin, should be started during the course of the study; except for rescue treatment allowed in Period 2 (see Section 5.2.3.4).

Investigational Drugs

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

Vaccines

Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. If the subject and investigator choose to administer live vaccines, these vaccinations must be completed per local label or at least 4 weeks (8 weeks in Japan), whichever is longer, before the first dose of study drug with appropriate precautions. Live vaccines are NOT allowed during study participation and including up to 4 weeks after the last dose of study drug. Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Herpes zoster;
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;

- Bacille Calmette-Guérin (BCG);
- Typhoid.

Examples of common vaccines that are inactivated, toxoid or biosynthetic, include but are not limited to: injectable influenza vaccine, pneumococcal and, pertussis ((Tdap) vaccines).

Cannabis

Concomitant use of medicinal and recreational cannabis is prohibited during the study.

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors or strong CYP3A inducers is excluded from the Screening Visit through the end of the study. The most common strong CYP3A inhibitors and inducers are listed in [Table 1](#).

Traditional Chinese Medicine

Traditional Chinese medicine is not permitted during the study, and subjects must have discontinued all traditional Chinese medicines at least 4 weeks prior to the first dose of study drug.

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

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir	Avasimibe
Clarithromycin	Carbamazepine
Conivaptan	Phenytoin
Grapefruit (fruit or juice)	Rifampin
Indinavir	St. John's Wort
Itraconazole	
Ketoconazole	
Lopinavir/Ritonavir	
Mibefradil	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

5.2.3.4 Rescue Therapy

For subjects re-randomized to placebo, ABT-494 7.5 mg QD or ABT-494 15 mg QD in Period 2, blinded rescue therapy with ABT-494 30 mg QD will be provided after the first instance of a < EASI 50 response starting at the Week 20 visit (4 weeks after re-randomization into Period 2). These subjects will continue on ABT-494 30 mg QD for the remainder of the study.

During Period 2, concomitant class III – IV, medium potency topical corticosteroid treatment will be permitted at the Week 24 visit and thereafter in subjects after a second instance of < EASI 50 response in any two Period 2 study visits beginning from Week 20. For subjects who receive topical corticosteroid rescue therapy, an additional visit will be

required 4 weeks after receiving topical corticosteroid rescue therapy. Discontinuation from study drug will be mandatory for subjects with < EASI 50 response compared with their Baseline EASI score 4 weeks following rescue with topical corticosteroids or at any visit thereafter.

Topical treatment allowed is limited to up to twice daily triamcinolone acetonide 0.1% cream or up to once daily mometasone furoate 0.1% cream. Use of a topical corticosteroid treatment should be recorded on the appropriate concomitant medication eCRF.

5.2.4 Contraception Recommendations

Contraception Recommendation for Females

A woman who is postmenopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Postmenopausal is defined as:

- Age \geq 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age < 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.

If the female subject is < 55 years of age:

AND has had no menses for \geq 12 months AND has no history of permanent surgical sterilization (defined above), FSH should be tested at Screening.

- If FSH is not tested, it is assumed that the subject is of childbearing potential and protocol-specified contraception is required.
- If the FSH is tested and the result is consistent with post-menopausal status, contraception is not required.

- If the FSH is tested and the result is consistent with pre-menopausal status, contraception is required, and a serum pregnancy test must be performed (see Section 5.3.1.1 pregnancy test).

For a female subject at any age:

- Female subjects with menses within the past 12 months are of childbearing potential and FSH is therefore not required but contraception is required.
- Female subject who are surgically sterile (defined above) are not of childbearing potential and therefore no FSH testing or contraception is required.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control that is effective from Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 30 days prior to Baseline Visit.
- Bilateral tubal occlusion/ligation (Japan only: bilateral tubal ligation only).
- Vasectomized partner(s) provided the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the women of childbearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Additional local requirements may apply. Refer to [Appendix P](#) for local requirements in Canada.

Contraception Recommendation for Males

For a male subject who has a female partner who is postmenopausal or permanently sterile, no contraception is required.

A male subject who is sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 30 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).
- OR
- True abstinence: Refraining from heterosexual intercourse-when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, male subjects must agree not to donate sperm from the Baseline Visit through 30 days after the last dose of study drug.

Male subjects are responsible for informing his partner(s) of the risk of becoming pregnant and for reporting any pregnancy to the study doctor. If a pregnancy occurs, a partner authorization form requesting pregnancy outcome information will be requested from the pregnant partner.

It is important to note that contraception recommendations described above are specifically intended to prevent pregnancy during exposure to the investigational therapies.

Additional local requirements may apply. Refer to [Appendix P](#) for local requirements in Canada.

5.3 Efficacy, Pharmacokinetic, Specific Cellular Pharmacodynamic Changes, Exploratory Research and Validation Studies, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in [Table 2](#).

Table 2. Study Activities

Activity	Screening D -35 to D -1	BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Every 12 Weeks ^x or PD ^a	4 Weeks Post Topical Rescue Visit ^y	30-Day F/U Visit ^a
Informed consent ^c	X													
Inclusion/exclusion criteria	X	X												
EASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCORAD		X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol and nicotine use	X													
Patient questionnaires ^d DLQI		X					X				X	X		
Patient questionnaires ^d Daily Pruritus NRS, PGIS, ADerm-SS, and ADerm-IS	X	X	X	X	X	X	X	X	X	X	X	X		X ^d
Patient questionnaires ^d MOS Sleep Scale POEM		X					X		X		X	X ^d		X
Patient questionnaires ^{d,e} Asthma Symptoms and Daytime Nasal Symptoms	X	X					X				X			
Actigraphy Device Download		X	X	X	X	X	X							
Medical/surgical history ^f	X	X												

Table 2. Study Activities (Continued)

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Every 12 Weeks ^x or PD ^a	4 Weeks Post Topical Rescue Visit ^y	30-Day F/U Visit ^a
AE assessment ^g	D -35 to D -1	D1 ^b	X	X	X	X	X	X	X	X	X	X	X	X
Only SAEs and Protocol-related nonserious AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Latent TB risk factor questionnaire ^h	X													
Central lab QuantIFERON-TB Gold test (or local PPD skin test) ^h	X													
Chest x-ray ^j	X													
12-lead ECG ^j	X						X							
Height (screening only) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^k	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam ^l	X	X					X		X		X	X		
Serum pregnancy test at central lab ^m	X										X	X ^m		
Pregnancy test ^{n,o}		X	X	X	X	X	X	X	X	X	X	X	X	X
Lab Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hsCRP ^p														
Blood chemistry ^q														
Hematology (CBC)														
Urinalysis ^r														

Table 2. Study Activities (Continued)

Activity	Screening	BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Every 12 Weeks ^x or PD ^a	4 Weeks Post Topical Rescue Visit ^y	30-Day F/U Visit ^a
HIV ¹ /HBV/HCV screenings	X					X ^s			X ^s					
Blood samples for ABT-494 PK assay			X ^u	X ^u	X ^v									
Blood samples for TBNK immunophenotyping		X			X		X	X						
Blood samples for exploratory research and validation studies (optional for some sites – see table for optional samples below) ^w		X	X	X			X	X						
Skin biopsies for exploratory research and validation studies (optional for some sites – see Table 3 for optional samples below) ^w		X					X							
Study Drug Dispensing/Administration		X		X	X	X	X	X	X	X	X	X ^z		
Dispense hand-held ePRO (includes subject diary) and actigraphy device	X													
Subject Diary Review			X	X	X	X	X	X	X	X	X			

Table 2. Study Activities (Continued)

- ADerm-IS = Atopic Dermatitis Impact Scale; ADerm-SS = Atopic Dermatitis Symptom Scale; BL = Baseline Visit; BSA = body surface area; CBC = complete blood count; D = Day; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; F/U = Follow-Up; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C reactive protein; IGA = Investigator's Global Assessment; MOS = Medical Outcomes Study; NRS = Numerical Rating Scale (for pruritus); PD = Premature Discontinuation; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; PPD = purified protein derivative; PtGA = Patient's Global Assessment; SAE = serious adverse event; SCORAD = Scoring atopic dermatitis; TB = tuberculosis; Wk = Week
- a. This visit is 30 days (\pm 3 days) after last dose of study drug. For those subjects who prematurely discontinue the study, if the subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) may occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. If a subject is discontinued from study drug, the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation.
 - b. The Baseline visit procedures will serve as the reference for all subsequent visits with the exception of the ECG which will be obtained at Screening only and used as the baseline reference.
 - c. Obtain prior to performing any study-related procedures.
 - d. Prior to other procedures; except for the questionnaires on the electronic hand-held device given to subjects to take home at Screening: daily Pruritus NRS, ADerm-SS and ADerm-IS Hand-held device usage stops at the Week 40 visit. Starting at the Week 52 visit, the questionnaires on the hand-held device (Pruritus NRS, ADerm-SS and ADerm-IS) will be given on the tablet during site visits. The MOS Sleep Scale questionnaire will stop at the Week 40 visit. The PGIS, POEM and DLQI questionnaires will be given on the tablet at site visits throughout the study.
 - e. Asthma Symptoms and Daytime Nasal Symptoms questionnaires are collected only for subjects with symptoms of asthma or rhinitis, respectively, at Screening and stop at the Week 40 visit.
 - f. Also note herpes zoster and hepatitis B vaccination status in medical history.
 - g. Collect SAEs and protocol-related nonserious AEs that occur after a subject signs the informed consent, prior to the first dose of study drug.
 - h. Refer to Section 5.3.1.1 Study Procedures TB Testing for specific requirements for TB testing and TB prophylaxis.
 - i. The screening chest x-ray will not be required if a subject had a previous normal chest-x-ray within 90 days of Screening, provided that all source documentation is available at the site.
 - j. For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all source documentation is available.
 - k. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

Table 2. Study Activities (Continued)

- l. A full physical exam is required at the visits indicated. A symptom-directed physical exam may be performed when necessary.
- m. For all females, collect serum for pregnancy test at screening and the Week 88 or PD visit. If serum pregnancy test comes back indeterminate or positive, a repeat test is necessary (pregnancy is an exclusion criterion); see Section 5.3.1.1 and Section 6.1.6 for details.
- n. Urine pregnancy test will be performed locally at every visit for all women of childbearing potential. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study.
- o. If time between visits is longer than 1 month, then collect the results of the monthly at home urine pregnancy test between scheduled visits (see Section 5.3.1.1). If a urine pregnancy test is positive, the subject must stop dosing, come in to the clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory. A pregnant or breastfeeding female will not be eligible for participation or continuation in this study. The monthly at home tests between scheduled on-site visits are to occur at Weeks 28 and 36; unless an on-site visit is necessary due to rescue therapy with topical corticosteroids per Section 5.2.3.4.
- p. hsCRP results will remain blinded to the Sponsor, Investigator, study site personnel, and subject for all visits except Screening. Investigators should refrain from locally and periodically testing hsCRP and serum amyloid A. Investigators should also refrain from locally testing procalcitonin except for safety evaluations of signs and symptoms of infection or adverse events.
- q. Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- r. A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.
- s. For Japan only: for subjects with HBs Ab+ and/or HBc Ab+ at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting at Week 12 and Week 24 is not necessary for subjects that have a history of HBV vaccine and are HBs Ab+.
- t. HIV testing will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If the result is confirmed as positive, then the Investigator will discuss with the subject potential implications to the subject's health and next steps. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. This testing is to be done at the central lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.
- u. At Week 2 and Week 4 visits, PK samples should be collected prior to dosing and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample will be collected at any time during the visit.

Table 2. Study Activities (Continued)

- v. PK samples will be collected at any time during the visit. Subject should follow the regular dosing schedule.
- w. Samples only collected if subject provides written consent. Subjects should be in fasting condition (8 hours, except for water) prior to samples collection. For selected sites, these assessments (blood samples and skin biopsies collection) will be made mandatory as part of the main study.
- x. Visits are every 12 weeks from the Week 40 visit to the Week 88 visit (Wk 52, Wk 64, Wk 76, and Wk 88).
- y. A visit will be required 4 weeks after receiving topical rescue therapy. After this visit, patients will continue to follow the standard protocol visit schedule, as applicable from that date (Wk 32, Wk 40, Wk 52, Wk 64, Wk 76, and Wk 88).
- z. Study Drug Dispensing stops at the Week 76 visit.

Note 1: Visit window is ± 3 days for Period 1 (Weeks 2, 4, 8, 12 and 16) and ± 5 days for Period 2 (Weeks 20, 24, 32, 40, 52, 64, 76 and 88) and a visit 4 weeks following topical rescue if applicable. Any of the procedures may be performed at the discretion of the investigator. Subjects who choose to discontinue study drug treatment, but continue to participate in the study, should complete a Premature Discontinuation Visit (PD Visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood and skin sample collection for exploratory research and validation studies. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply.

Note 2: Twice daily use of an additive-free, bland emollient is required for at least 7 days prior to Baseline and during the study.

Table 3. Study Activities – Optional and Mandatory Samples for Exploratory Research and Validation Studies

Activity	Screening D -30 to D -1	BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Every 12 Weeks or PD ^a D365 – D617	4 Weeks Post Topical Rescue Visit	30- Day F/U Visit
Pharmacogenetic samples ^a		X												
Epigenetic samples ^a		X	X	X			X	X						
Transcriptomic and epigenetic samples ^a		X	X	X			X	X						
Plasma samples for analyses including, but not limited to, proteomic and targeted protein investigations ^a		X	X	X			X	X						
Serum samples for analyses including, but not limited to, proteomic and targeted protein investigations ^a		X	X	X			X	X						
Sample for PBMC assays ^a		X		X			X							
Skin Biopsies for analyses including, but not limited to, epigenetics, transcriptomics, proteomics, immunohistochemistry ^{a,b} and targeted investigations		X		X			X							

BL = Baseline Visit; D = Day; F/U = Follow-Up; PBMC = Peripheral Blood Mononuclear Cell; PD = Premature Discontinuation; Wk = Week

- a. Based on the value of the different technologies, samples may also be used to assess other biomarker signatures, including but not limited to metabolomics, lipidomics, and other approaches. Samples may be used for assay of study drugs if needed.
- b. Subjects may still participate in the optional exploratory research/validation studies if they decide not to participate in this optional collection of biopsies. In selected sites all samples in Table 3, including biopsies, will be made mandatory as part of the main study.

Table 3. Study Activities – Optional and Mandatory Samples for Exploratory Research and Validation Studies (Continued)

Note 1: Collections to be performed only if subject provides separate written consent to collect the exploratory research/validation studies samples; if the consent is not signed, no samples can be collected. It is preferred that the subject has fasted (8 hours, except for water) prior to sample collection, however it is not required. It must be recorded whether the subject has fasted or not at the time of collection.

Note 2: Selected sites will be asked to perform a complete investigation of biomarkers. For such sites, all samples in [Table 3](#) will be made mandatory as part of the main study. There will be a specific ICF for subjects in these selected sites.

5.3.1.1 Study Procedures

The study procedures outlined in [Table 2](#) are discussed in detail in this section, with the exception of exploratory research and validation studies (discussed in [Section 5.3.1.2](#)), drug concentration measurements (discussed in [Section 5.3.2](#)), the collection of prior and concomitant medication information (discussed in [Section 5.2.3](#)), and the collection of AE information (discussed in [Section 6.1.1](#)). All study data will be recorded in source documents and on the appropriate eCRFs.

Informed Consent

At the Screening visit, the subject will sign and date a study specific, IEC/IRB approved, informed consent form before any study procedures are performed or any medications are withheld from the subject in order to participate in this study. Separate written consent will be required for each subject in order to participate in the optional exploratory research and validation studies. Details regarding how informed consent will be obtained and documented are provided in [Section 9.3](#).

Inclusion/Exclusion Criteria

Subjects will be evaluated to ensure they meet all inclusion criteria and have none of the exclusion criteria at both Screening and Baseline Visits.

Medical and Surgical History

A complete non-AD medical and surgical history, including history of alcohol and nicotine use, will be taken from each subject at the Screening visit.

Additionally, a list of each subject's specific AD related medical and surgical history should be recorded at Screening. History of clinical herpes zoster, herpes zoster vaccination, and hepatitis B vaccination status will be recorded as part of the medical history. An updated medical history will be obtained prior to study drug administration at Baseline/Day 1, to ensure the subject is still eligible for enrollment.

A detailed medical history with respect to TB risk factors will be documented in the study source documentation. This information will include BCG vaccination, cohabitation with individuals who have had TB, and travel to, residence in, or work in TB endemic locations.

Atopic Dermatitis Investigator Evaluations

Body Surface Area (BSA)

A qualified investigator should select the subject's right or left hand as the measuring device. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1%. Measurement of the total area of involvement by the physician is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved. The site should make every attempt to have the same qualified Investigator or designee perform all BSA assessments on a given subject throughout the study and are to be performed as specified in [Table 2](#).

Eczema Area and Severity Index (EASI)

A qualified investigator will perform the EASI assessment ([Appendix E](#)). The site should make every attempt to have the same qualified Investigator or designee perform all EASI assessments on a given subject throughout the study, following the schedule in [Table 2](#).

Investigator's Global Assessment for Atopic Dermatitis (IGA)

A qualified investigator will perform the IGA assessment ([Appendix D](#)). The site should make every attempt to have the same qualified Investigator or designee perform all IGA assessments on a given subject throughout the study and are to be performed as specified in [Table 2](#).

SCORing Atopic Dermatitis (SCORAD)

A qualified investigator will perform the SCORAD assessment ([Appendix F](#)). The site should make every attempt to have the same qualified Investigator or designee perform all

SCORAD assessments on a given subject throughout the study and are to be performed as specified in [Table 2](#); via an electronic tablet device provided to sites.

Patient Questionnaires

Subjects will complete the following questionnaires as specified in [Table 2](#):

- Dermatology Life Quality Index (DLQI) ([Appendix G](#))
- Daily Pruritus (itch) Numerical Rating Scale (NRS) ([Appendix H](#))
- Medical Outcomes Study (MOS) Sleep Scale ([Appendix I](#))
- Patient Oriented Eczema Measure (POEM) ([Appendix J](#))
- Asthma Symptoms Questionnaire (only for subjects with asthma symptoms) ([Appendix K](#))
- Daytime Nasal Symptoms Questionnaire (only for subjects with rhinitis symptoms) ([Appendix L](#))
- Atopic Dermatitis Symptom Scale (ADerm-SS) ([Appendix M](#))
- Atopic Dermatitis Impact Scale (ADerm-IS) ([Appendix N](#))
- Patient Global Impression of Severity (PGIS) ([Appendix O](#))

All patient-reported outcomes (PROs) are collected electronically (discussed in [Section 10.2](#)).

The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with clinical site personnel has occurred to avoid biasing the subject's response; except for the questionnaires on the electronic hand-held device (daily Pruritus NRS, [REDACTED] ADerm-SS and ADerm-IS).

Hand-held device usage stops at the Week 40 visit. Starting at the Week 52 visit, the questionnaires on the hand-held device (Pruritus NRS, ADerm-SS and ADerm-IS) will be given on the tablet during site visits. The MOS Sleep Scale questionnaire will stop at the Week 40 visit. The PGIS, POEM and DLQI questionnaires will be given on the tablet throughout the study as specified in [Table 2](#).

Asthma Symptoms and Daytime Nasal Symptoms questionnaires are collected only for subjects with symptoms of asthma or rhinitis, respectively, at Screening and stop at the Week 40 visit.

TB Testing

The TB screening tests are diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB.

All subjects will be assessed for evidence of increased risk for TB by a risk assessment form ([Appendix C](#)) and tested for TB infection by QuantiFERON-TB Gold Test. The PPD Skin Test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines). The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF.

- Preferred Method: QuantiFERON-TB Gold Test will be analyzed by the central laboratory (QuantiFERON test is preferred over PPD skin test).
- If QuantiFERON-TB Gold Test is NOT possible (or if both an Interferon-Gamma Release Assays [IGRA] and PPD Skin Test are required per local guidelines): the PPD Skin Test (also known as a TB Skin Test) will be performed according to standard clinical practice. The TB Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm for AD subjects is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.

If a subject had a negative QuantiFERON-TB Gold (or PPD) test (or IGRA equivalent such as T-SPOT TB test) within 90 days prior to Screening and source documentation is available, the test does not need to be repeated, provided nothing has changed in the

subject's medical history to warrant a repeat test. These cases must be brought to the attention of the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director and provide a recommendation. The results of the TB test(s) will be retained at the site as the original source documentation.

In the event both a PPD test and a QuantiFERON-TB Gold test are performed, the result of the QuantiFERON-TB Gold test will supersede the result of the PPD test, unless otherwise required by local guidelines. If the QuantiFERON-TB Gold test is indeterminate, the site should repeat the test with another blood sample. If the second QuantiFERON-TB Gold test is also indeterminate, the subject is considered to be positive.

Subjects with a negative QuantiFERON[®]-TB Gold test (OR negative PPD TB skin test) and chest x-ray (CXR) not suggestive of active TB or prior TB exposure may be enrolled. Any positive TB screen after the subject has started the study, should be reported as an adverse event of latent TB (in the absence of an adverse event of active TB).

If the subject has evidence of a latent TB infection (QuantiFERON[®]-TB Gold test or the PPD test positive and the subject has a CXR not suggestive of active TB), prophylactic treatment must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). The prophylaxis needs to be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug. If the Investigator deems that it is necessary, consultation with a TB expert could be considered.

Of note: Rifampicin is not allowed for TB prophylaxis.

Subjects with a prior history of latent TB that have documented completion of a full course of anti-TB therapy within 1 year prior to first study drug administration will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment.

Subjects with a documented completion of a full course of anti-TB therapy greater than 1 year prior to first study drug administration may be allowed to enter the study only after

consultation with the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director and provide a recommendation.

Newly initiated prophylactic treatment should be captured on the concomitant medications page in the eCRF and in the source documents. Prior therapy should be captured in the eCRF.

Chest X-Ray (CXR)

A CXR (posterior-anterior and lateral views) is required for all subjects at Screening to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal CXR (posterior-anterior and lateral views) within 90 days of Screening, provided all source documentation is available at the site as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test.

Subjects can have a repeat CXR at any time during the study as warranted, based on the opinion of the Investigator.

Only qualified personnel must perform an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the Principal Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Investigator must contact the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director before enrolling the subject.

12-Lead ECG

A resting 12-lead ECG will be performed at the designated study visits as specified in [Table 2](#). A qualified physician will interpret the clinical significance of any abnormal

finding, sign, and date each ECG. ECG with QT interval corrected for heart rate using Friedericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate eCRF if QTcF prolongation is observed. In these cases, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible site monitor and kept with subject's source documents onsite.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided source documentation is available. If there are other findings that are clinically significant, the Investigator must bring this to the attention of the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director and provide a recommendation before the subject can be enrolled.

Subjects can have a repeat ECG at any time during the study as warranted, based on the opinion of the Investigator.

Height and Weight

Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits, as specified in [Table 2](#). All measurements will be recorded in metric units where applicable.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate (counted for at least 30 seconds after 5 minutes in sitting position), respiratory rate, and body temperature will be obtained at visits specified in [Table 2](#). Blood pressure, pulse rate, body temperature, and respiratory rate should be measured before blood draws are performed.

Physical Examination

A complete physical examination will be performed at the designated study visits as specified in [Table 2](#). The physical examination at the Baseline Visit will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted by the Investigator at Baseline prior to the first dose of study drug will be recorded in the subject's medical history; abnormalities noted after the first dose of study drug will be evaluated and documented by the Investigator as to whether or not the abnormality is an AE (see Section [6.1.1](#) for AE definition). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

Pregnancy Test

A serum pregnancy test will be performed for all female subjects of child bearing potential at the Screening Visit and the Week 88 or PD visit. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is indeterminate, it should be repeated ≥ 3 days later to determine eligibility. If the repeat serum pregnancy test is:

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

A urine pregnancy test will be performed for all female subjects of childbearing potential at the Baseline Visit prior to the first dose of study drug and at all subsequent visits. More

frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

- If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required.
- If a urine pregnancy test post baseline is positive, study drug needs to be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be permanently discontinued.

In Period 2, for women of childbearing potential, a urine pregnancy test will be performed at all visits and monthly at home between scheduled study visits (at Weeks 28 and 36 at home, unless an on-site visit is necessary due to rescue therapy with topical corticosteroids per Section 5.2.3.4). The results of the monthly at home tests will be communicated to the site. If a urine pregnancy test is positive, the subject must stop dosing, come in to the clinic and have blood drawn for a serum pregnancy test that will be analyzed at the central laboratory.

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

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

Clinical Laboratory Tests

Blood and urine samples will be obtained for clinical laboratory tests listed in [Table 4](#). Samples will be obtained at the designated study visits in [Table 2](#).

Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per Investigator's discretion. A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

The central laboratory chosen for this study will provide instructions regarding the collection, processing, and shipping of these samples.

Blood draws should be performed after all clinical assessments and questionnaires and vital sign determinations have been completed; but before any study drug administration during a visit.

For clinic visits where samples for serum chemistry and/or advanced lipid panel tests are collected, subjects should be fasting (a minimum 8-hour fast) whenever possible. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.

Urine samples will be obtained for urinalysis testing at visits specified in [Table 2](#). The central laboratory will be responsible for performing a macroscopic urinalysis (urine dipstick) on the collected urine specimens. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant the Investigator should apply the standard of care for medical

evaluation and treatment per local guidelines (see Section 6.1.7 for toxicity management guidelines):

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

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

Table 4. Clinical Laboratory Tests

Hematology	Clinical Chemistry ^a	Urinalysis ^b	Other Laboratory Tests
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity	<u>Central Lab Tests:</u>
Hemoglobin	Creatinine	Ketones	Serum Pregnancy (bHCG)
RBC count	Total bilirubin	pH	test ^d
WBC count	INR (reflex only) ^c	Protein	HBsAg ^e
Neutrophils	Albumin	Blood	HBsAb ^e
Bands	Aspartate aminotransferase	Glucose	HBcAb ^e
Lymphocytes	(AST)	Urobilinogen	HBV DNA PCR reflex only ^e
Monocytes	Alanine aminotransferase	Bilirubin	HCV Ab ^e
Basophils	(ALT)	Leukocytes	HCV RNA reflex only ^e
Eosinophils	Alkaline phosphatase	Nitrites	HIV Ab ⁱ
Platelet count	CPK	Microscopic	QuantiFERON-TB Gold
	Sodium	examination,	High sensitivity CRP
	Potassium	if needed	(hs-CRP) ^f
	Bicarbonate/CO ₂		FSHi ^g
	Chloride		<u>Local Lab Tests:</u>
	Calcium		Urine pregnancy test ^h
	Inorganic phosphate		
	Uric acid		
	Total protein		
	Glucose		
	Cholesterol		
	LDL-C		
	HDL-C		
	Triglycerides		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; bHCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; FSH = Follicle-Stimulating Hormone; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C virus antibody; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high sensitivity C-reactive protein; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; PCR = polymerase chain reaction; pH = RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; WBC = white blood cell

- Minimum 8-hour fast. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation.
- A urine dipstick macroscopic urinalysis will be completed by the central laboratory at all required visits. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.
- INR will only be measured if ALT and/or AST > 3 × ULN.
- A serum pregnancy test will be performed for all female subjects at the Screening Visit and if postbaseline urine pregnancy test turns positive.

Table 4. Clinical Laboratory Tests (Continued)

- e. At Screening only. For Japan only: for subjects with HBs Ab+ and/or HBc Ab+ at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and are HBs Ab+.
- f. The hs-CRP results starting from Baseline (Day 1) will not be reported to the Sponsor, Investigator, study site personnel, and the subject. For safety evaluations of signs and symptoms of infection and management of adverse events, the investigator may locally test procalcitonin. Results of tests such as hsCRP, serum amyloid A and procalcitonin may be blunted in subjects taking a JAK inhibitor, thereby limiting the clinical utility of these tests in the setting of a possible safety assessment or adverse event management. Any hsCRP, CRP, serial serum amyloid A, or serial procalcitonin local tests reported to the investigator will be recorded as protocol deviations.
- g. At screening for female subjects < 55 years old.
- h. A urine pregnancy test will be performed for all female subjects at the Baseline Visit prior to the first dose of study drug and all subsequent visits. If the baseline urine pregnancy test performed at the site is negative, then dosing with study drug may begin. If the baseline urine pregnancy test performed at the site is positive, dosing with study drug must be withheld and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be withheld and the subject must be discontinued from the study. In the event a pregnancy test comes back borderline, a repeat test is required. If a urine pregnancy test postbaseline is positive, study drug needs to be temporarily discontinued and a serum pregnancy test is required. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, study drug must be permanently discontinued.
- i. Anti-HIV Ab will be performed at Screening. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. This testing is to be done at the central lab. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Hepatitis Screen:

All subjects will be tested for the presence of HBV and HCV at Screening.

Hepatitis B:

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

HBs Ag

HBc Ab/anti-HBc

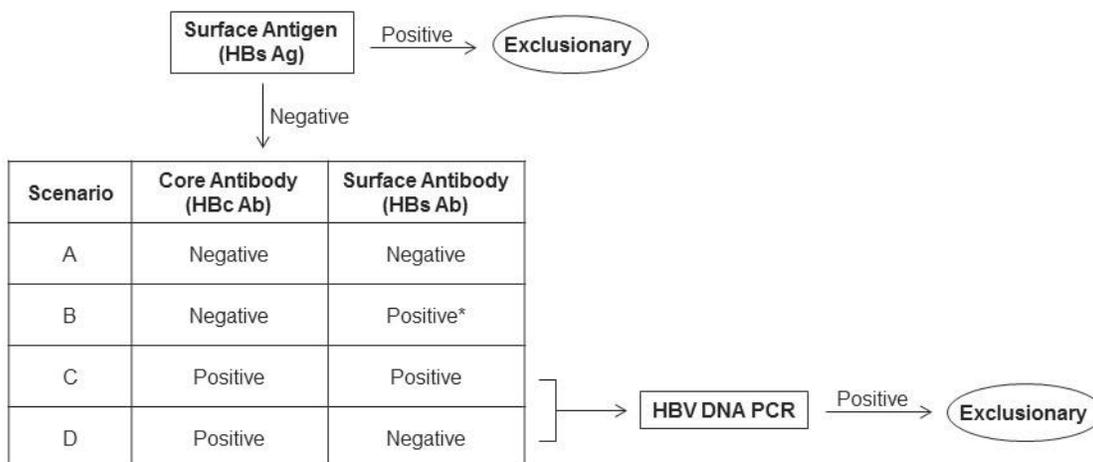
HBs Ab/anti-HBs (Hepatitis B surface antibody)

A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will be tested (automatic reflex testing) for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

- A negative test result for HBc Ab does **not** require HBV DNA PCR qualitative testing and the subject may be enrolled (Figure 2, Scenarios A and B). For a subject who has had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected and the subject may be enrolled (Figure 2, Scenario B).*
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 2), (Scenarios C and D).
 - A positive result for HBV DNA or a result that exceeds detection sensitivity will be exclusionary.
 - A subject with a negative result for HBV DNA testing may be enrolled.
 - For Japan only: for subjects with HBs Ab+ and/or HBc Ab+ at Screening, the HBV-DNA PCR test should be performed again at Week 12 and Week 24. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting at Week 12 and Week 24 is not necessary with subjects that have a history of HBV vaccine and are HBs Ab+.

Figure 2. Criteria for HBV DNA PCR Qualitative Testing



* For subjects who have had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected and these subjects may be enrolled.

Hepatitis C:

All subjects will be tested for the presence of Hepatitis C Virus antibodies (HCV Ab) at Screening. Samples positive for HCV Ab require PCR qualitative testing for HCV RNA. Any HCV RNA PCR result that meets or exceeds detection sensitivity will be exclusionary. Subjects with a history of treated HCV infection may be allowed to enroll if documentation of effective treatment is available and no evidence of HCV is detected by HCV RNA PCR.

TBNK Assessment By Immunophenotyping

Blood samples will be collected at the Baseline, Week 8, Week 16, and Week 20, visits and will be utilized to assess effects of JAK inhibition on certain leukocyte subsets, including T (CD4+ and CD8+) cells, B (CD19+) cells, natural killer (NK) cells, and natural killer-T (NKT) cells. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

HIV

Subjects with HIV infection are excluded from study participation. HIV testing will be performed at Screening. This testing is to be done at the central lab. The Investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the Investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study participation if the test results indicate a positive HIV infection. AbbVie will not receive results from the testing and will not be made aware of any positive result.

Randomization/Drug Assignment

All Screening laboratory results must be reviewed, signed, and dated by the Principal Investigator or Sub-investigator prior to the Baseline Visit. Subjects will not be enrolled into the study if laboratory or other Screening result abnormalities are deemed clinically significant by the Principal Investigator or Sub-investigator.

Subjects will be eligible for randomization if they continue to meet all of the selection criteria (Section 5.2) at Baseline and are willing to continue in the study.

In Period 1, at the Baseline visit, subjects will be randomized in a 1:1.1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Group 1: ABT-494 7.5 mg QD for 16 weeks
- Group 2: ABT-494 15 mg QD for 16 weeks
- Group 3: ABT-494 30 mg QD for 16 weeks
- Group 4: Matching Placebo for 16 weeks

Randomization will be stratified by geographic region (US/PR/Canada, EU/AUS, and Japan). Enrollment in Japan will be capped at 10% of subjects (approximately 4 subjects per group).

In Period 2, at the Week 16 visit, all subjects will be re-randomized in a 1:1 ratio using interactive response technology (IRT) to receive double-blind study drug in one of the following treatment groups:

- Subjects from Group 1 in Period 1: ABT-494 7.5 mg QD or matching placebo for 24 weeks
- Subjects from Group 2 in Period 1: ABT-494 15 mg QD or matching placebo for 24 weeks
- Subjects from Group 3 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks
- Subjects from Group 4 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks

During Period 2, starting at the Week 20 visit, subjects re-randomized to placebo, ABT-494 7.5 mg QD or ABT-494 15 mg QD will be reassigned in a blinded manner to ABT-494 30 mg QD if at any visit their response is < EASI 50. These subjects will continue on ABT-494 30 mg QD for the remainder of the study.

See Section 5.5.3 for details.

Study Drug Dispensing, Dosing, and Compliance

Study drug and Dosing Diary will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Table 2. The first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed. Subjects will maintain an electronic dosing diary for all study medication administered outside of the study visit, (e.g., at home) to capture dosing dates and times. At all visits, except Baseline, Week 2, 4-week follow-up visit after topical corticosteroid rescue in Period 2, and the 30-day follow-up visit, the site personnel will review the electronic diary data, returned study drug kits, and

empty study drug packaging to verify compliance. Electronic diary data stops at the Week 40 visit.

(Refer to Section 5.5 for additional information.)

Actigraphy Device

During the Screening Visit, subjects will be dispensed two actigraphy devices and will be trained on how and when to wear the devices by site staff. Subjects will be instructed to wear two actigraphy watch-type devices (one on each wrist) at bedtime daily during their whole daily rest (sleep) period (see Section 10.2 for more detail). Data will be collected from the day of the Screening visit through the Week 16 visit (see Table 2 for visits requiring data download).

5.3.1.2 Collection and Handling of Optional and Mandatory Samples for Exploratory Research and Validation Studies

5.3.1.2.1 Samples for Exploratory Research Variables and Validation Studies

Subjects will have the option to provide samples for exploratory research and validation studies. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research/validation study.

Exploratory research can help to improve our understanding of how individuals respond to drugs and our ability to predict which subjects would benefit from receiving specific therapies. In addition, exploratory research may help to improve our understanding of how to diagnose and assess/monitor AD by assessing associations between disease characteristics, outcomes data, and biomarkers of interest.

Validation studies, including those related to the development of potential in-vitro diagnostic tests, may be carried out retrospectively in order to assess associations between events of interest (i.e., efficacy and/or safety events) and candidate biomarkers.

For Japan only: research on DNA and RNA exploratory research samples will be restricted to treatment response of pharmacokinetics, efficacy, tolerability, and safety.

AbbVie (or people or companies working with AbbVie) will store the exploratory research/validation studies samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-494 (or drugs of this class) or AD and related conditions continues, but for no longer than 20 years after study completion.

All subjects are preferred to have been fasting for a minimum of 8 hours prior to sample collection. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation. The following samples will be collected according to [Table 3](#) for each subject who consents to provide samples for exploratory research/validation studies:

- DNA samples for pharmacogenetic or epigenetic analyses;
- RNA samples for transcriptomic and/or epigenetic analyses;
- Serum and plasma samples for systemic analyses, including but not limited to proteomic and metabolomics (these samples may be used for assay of study drugs if needed);
- Blood samples for peripheral blood mononuclear cell (PBMC) investigations;
- Skin biopsies for pathological and biological investigations, including, but not limited to transcriptomics, proteomic profiling, immunohistochemistry (IHC), and targeted investigations, e.g., identification of specific analytes, and target identification.

The procedures for obtaining and documenting informed consent are discussed in [Section 9.3](#).

Samples will be shipped to AbbVie or a designated laboratory for RNA/DNA extraction, if applicable, and/or analyses or long-term storage. Instructions for the preparation and shipment of the samples will be provided in the laboratory manual.

Skin Biopsy samples for investigations that include, but are not limited to, epigenetics, transcriptomics, proteomics, IHC and targeted investigations.

For subjects who consent, 2 skin biopsies should be collected at the Baseline and Week 16 visits (one lesional and one non-lesional from the same general area at each visit) and one lesional skin biopsy at the Week 4 visit. Skin biopsies should be between 4.5 and 5 millimeters. Non-lesional skin biopsies should be at least 1.5 centimeters away from the lesional biopsied area and in the same general area. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Samples will be shipped to AbbVie or a designated laboratory for extraction, if applicable and/or analyses and/or long-term storage. Instructions for the preparation and shipment of the samples will be provided in a laboratory manual.

Mandatory Exploratory Research/Validation Studies Samples Collection From Selected Sites

Selected sites will be asked to perform a complete investigation of biomarkers. For such sites, these assessments (blood sample and skin biopsy collections) will be made mandatory as part of the main study. There will be a specific ICF for subjects in these selected sites.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples (plasma) for pharmacokinetic (PK) assay of ABT-494 (upadacitinib) and possibly other medications will be collected as follows:

- At Weeks 2 and 4 prior to dosing;
- At Weeks 8, 12, 16, 20, 24, 32, 40, 52, 64, 76 and 88/PD at any time during the visit.

On Week 2 and Week 4 visit days, if possible, subjects should take the study drug dose at the clinic after collecting the PK blood sample, except if the subjects regularly take the study drug dose at night. Those subjects who regularly take the study drug dose at night should continue to take study drug according to their normal schedule. For all other visits, subjects can take the study drug dose on visit days at their regular schedule and not necessarily at the clinic.

For all PK samples, the date and accurate time of the PK sample collection will be recorded on the lab requisition form. The date and accurate time of the PK sample collection and the last two study drug doses will be recorded on the eCRF to the nearest minute.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.2 Measurement Method

Plasma concentrations of ABT-494 (upadacitinib) will be determined by the Drug Analysis Department at AbbVie using a validated liquid chromatography/mass spectrometry method.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variable

The primary endpoint is the mean percent (%) change from Baseline (Day 1) in EASI score at Week 16.

5.3.3.2 Secondary Variables

- Proportion of subjects achieving an EASI 75 response, defined as at least a 75% reduction in EASI score, at Week 16 relative to the Baseline (Day 1)
- Proportion of subjects achieving an Investigator Global Assessment (IGA) of "0" or "1" at Week 16

- Percent change from Baseline to Weeks 2, 8 and 16 in pruritus numerical rating scale (NRS)
- Percent change in EASI score from Baseline at Week 8
- Percent change in SCORAD score from Baseline at Weeks 8 and 16
- Proportion of subjects achieving EASI 50/75/90 response at Weeks 8 and 16
- Proportion of subjects achieving SCORAD 50/75/90 response at Weeks 8 and 16
- Proportion of subjects with Dermatology Life Quality Index (DLQI) = "0" or "1" at Weeks 8 and 16
- Change from Baseline in DLQI at Weeks 8 and 16
- Change and percent change from Week 16 (re-randomization) in EASI score at all Period 2 visits
- Time to loss of EASI 50 response relative to Baseline among those who were re-randomized as EASI 75 responders at Week 16
- Summary of EASI 75 at all visits in Period 2 among those who were re-randomized as EASI 75 non-responders at Week 16

5.3.3.3 Exploratory Variables

- Time to EASI 50/75/90 and IGA "0" or "1" response in Period 1
- Proportion of subjects achieving EASI 50/75/90/100 response at all visits
- Proportion of subjects achieving SCORAD 50/75/90 response at all visits
- Change from Baseline to Week 16 in Patient Oriented Eczema Measure (POEM)
- Change from Baseline to Week 16 in Medical Outcomes Study (MOS) Sleep Scale
- Change from Baseline to Week 16 in Asthma Symptoms Questionnaire
- Change from Baseline to Week 16 in Daytime Nasal Symptoms Questionnaire
- Change from Baseline in total sleep time per night (TST min), Sleep Efficiency (%), Wake After Sleep Onset (WASO), number of scratching

events per hour, mean activity during rest (sleep) periods as measured by actigraphy.

Primary and secondary variables will also be evaluated at all scheduled visits through Week 88.

5.3.4 Safety Variables

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, ECG, and clinical laboratory testing (hematology, chemistry, and urinalysis).

5.3.5 Pharmacokinetic Variables

Plasma ABT-494 (upadacitinib) concentrations will be measured at the times indicated in [Table 2](#). A non-linear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values for ABT-494 oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data.

5.3.6 Exploratory Research Variables and Validation Studies

Optional and mandatory (at selected sites only) samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to nucleic acids, proteins, lipids, or metabolites.

For Japan only: research on DNA and RNA exploratory research samples will be restricted to treatment response of pharmacokinetics, efficacy, tolerability, and safety.

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of AD or related conditions and/or ABT-494 or drugs of similar

classes. The results from these analyses are exploratory in nature and may not be included with the clinical study report (CSR).

The samples may also be used to develop new therapies, research methods or technologies. In addition, samples from this study may be stored for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

A subject may withdraw from the study at any time and for any reason. The Investigator may discontinue any subject's participation for any reason, including an AE, safety concerns, or failure to comply with the protocol. See Section 6.1.7 for toxicity management criteria.

Subjects will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator and the AbbVie Therapeutic Area Medical/Scientific Director.
- Serious infections (e.g., sepsis) which cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk for continued participation in the trial as determined by the Investigator in consultation with the AbbVie Therapeutic Area Medical/Scientific Director.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion or exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Therapeutic Area Medical/Scientific Director.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie Therapeutic Area Medical/Scientific Director.

- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial in consultation with the AbbVie Therapeutic Area Medical/Scientific Director.
- Subject develops a gastrointestinal perforation.
- Subjects with disease progression or not responding to treatment are to be withdrawn from the trial based on investigator's discretion.
- In Period 1, discontinuation from study drug will be mandatory for any subject with an EASI score worsening of 25% or more compared with their Baseline EASI score at any 2 consecutive study visits from Week 4 to Week 12.
- In Period 2, discontinuation from study drug will be mandatory for subjects with < EASI 50 response compared with their Baseline EASI score 4 weeks following rescue with topical corticosteroids or at any visit thereafter.

Discontinuation of Study Drug and Continuation of Study Participation

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment complete a Premature Discontinuation Visit (PD visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should continue to be followed for all regularly scheduled visits as outlined in [Table 2](#) on standard of care, unless they have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Subjects that choose to participate in the study after discontinuation of study drug treatment should follow the regular visit schedule as outlined in [Table 2](#); and adhere to all study procedures except for dispensing study drug, PK and exploratory research sample collection. In addition, all future rescue and efficacy-driven discontinuation criteria no longer apply.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD Visit should be completed as soon as possible, preferably within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy. In addition, if subject is willing, a 30-day follow-up on-site visit (or phone call if a visit is not possible) after the last dose of study drug may be completed to determine the status of any ongoing AEs/SAEs, the occurrence of any new AEs/SAEs, and medications used to treat AEs/SAEs.

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

Follow-Up Period

A follow-up visit (or phone call if a visit is not possible) should occur for all subjects approximately 30 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

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

Subjects who discontinue the study or study drug prematurely after randomization will not be replaced.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Study drug will be taken orally once daily beginning on Day 1 (Baseline). Subjects will be instructed to take one daily dose at approximately the same time each day. The study drug can be taken with or without food.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in [Table 5](#).

Table 5. Identity of Investigational Product

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABT-494 (upadacitinib)	oral	tablet	7.5 mg 15 mg 30 mg	AbbVie
Matching placebo	oral	tablet	NA	AbbVie

5.5.2.1 Packaging and Labeling

ABT-494 (upadacitinib) and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each bottle (kit) label will contain a unique kit

number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will be labeled as required per country requirements. Labels must remain affixed to the bottles (kits). All blank spaces on the label will be completed by the site staff prior to dispensing to the subjects.

5.5.2.2 Storage and Disposition of Study Drug

ABT-494 (upadacitinib) must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

Emollients

A commercially available skin moisturizer will be provided to subjects to maintain skin hydration. Emollients for subject use will be provided by AbbVie to study sites on a regular basis. See local product information for further instructions regarding recommended storage conditions and packaging configuration.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will be randomized using IRT. Before the study is initiated, IRT directions will be provided to each site.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. Subjects who meet the inclusion and none of the exclusion criteria defined in Section 5.2.1 and Section 5.2.2 will be randomized by IRT in in 1:1:1:1 ratio to one of four treatment groups: (1) ABT-494 7.5 mg, (2) ABT-494 15 mg, (3) ABT-494 30 mg or (4) matching placebo, once daily for 16 weeks in a double-blinded manner. The randomization will be stratified by geographic region (US/PR/Canada, EU/AUS, and Japan). 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 who complete Period 1 will be re-randomized at Week 16 within their original treatment group assignments to either ABT-494 or placebo into a 72-week double-blind, placebo controlled treatment period (Period 2) in a 1:1 ratio as shown in [Figure 1](#) (study design). Randomization will be stratified by geographic region and EASI 75 response at Week 16. In Period 2, at the Week 16 visit, all subjects will be re-randomized as follows:

- Subjects from Group 1 in Period 1: ABT-494 7.5 mg QD or matching placebo for 24 weeks
- Subjects from Group 2 in Period 1: ABT-494 15 mg QD or matching placebo for 24 weeks
- Subjects from Group 3 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks
- Subjects from Group 4 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks

During Period 2, starting at the Week 20 visit, subjects re-randomized to placebo, ABT-494 7.5 mg QD or ABT-494 15mg QD will be reassigned in a blinded manner to ABT-494 30 mg QD if at any visit their response is < EASI 50. These subjects will continue on ABT-494 30 mg QD for the remainder of the study.

IRT will provide the appropriate study drug kit number(s) to dispense to each subject. Study drug will be administered at the study visits as summarized in [Section 5.3.1.1](#). Returned study drug must not be re-dispensed to any subject.

5.5.4 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in [Section 5.5.1](#).

On dosing days that occur on study visit days, subjects should follow the regular dosing schedule (refer to [Section 5.3.2.1](#) regarding Week 2 and Week 4 visits).

Each subject's dosing schedule should be closely monitored by the site at each study visit by careful review of the subject's dosing diary. This will ensure that all subjects enrolled into the study maintain their original dosing schedule beginning with the first dose of study drug (Baseline/Day 1).

In Period 1, subjects will be randomized in a 1:1:1:1 ratio to one of four treatment groups: (1) ABT-494 7.5 mg, (2) ABT-494 15 mg, (3) ABT-494 30 mg or (4) matching placebo, once daily. Subjects who complete Period 1 will be re-randomized at Week 16 into the 72-week double-blind, placebo controlled treatment period (Period 2) in a 1:1 ratio as follows:

- Subjects from Group 1 in Period 1: ABT-494 7.5 mg QD or matching placebo for 24 weeks
- Subjects from Group 2 in Period 1: ABT-494 15 mg QD or matching placebo for 24 weeks
- Subjects from Group 3 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks
- Subjects from Group 4 in Period 1: ABT-494 30 mg QD or matching placebo for 24 weeks

During Period 2, starting at the Week 20 visit, subjects re-randomized to placebo, ABT-494 7.5 mg QD or ABT-494 15 mg QD will be reassigned in a blinded manner to ABT-494 30 mg QD if at any visit their response is < EASI 50. These subjects will continue on ABT-494 30 mg QD for the remainder of the study.

- If a subject should forget to take their ABT-494 (or matching placebo) dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.
- If the subject experiences a study drug interruption > 14 consecutive days in Period 1 or > 21 consecutive days in Period 2 (other than for reasons listed in

Section 6.1.7), they should notify their study site physician, and the subject should be discontinued from the study drug.

Before the study is initiated, directions for system use of the IRT will be provided to each site.

5.5.5 Blinding

Study sites and subjects will remain blinded for the duration of the study. To maintain integrity of the trial and avoid introduction of bias, the study team will only have access to unblinded subject level data for AEs of special interests and SAEs for regulatory submissions. In order to maintain the blind, the ABT-494 (upadacitinib) tablets and placebo 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 situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director and provide a recommendation prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the Therapeutic Area Scientific Director, 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 EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: <http://www.endpointclinical.com/helpdesk/>.

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

5.5.5.1 Blinding of Data for Data Monitoring Committee (DMC)

An external Data Monitoring Committee (DMC) comprised of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. If necessary to ensure subject safety, the DMC will also be given access to efficacy data. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, and relevant safety data to be assessed.

Communications from the DMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Subject dosing will be recorded on a subject dosing diary. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each clinic visit. The study site personnel will document compliance in the study source documents.

5.5.7 Drug Accountability

The Investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document and by registering the arrival of drug through the IRT. The original Proof of Receipt Note and the IRT confirmation sheet will be kept in the site files as a record of what was received.

In addition, an IRT will be used to document investigational product accountability including but not limited to date received, the lot number, kit number(s), date dispensed, subject number, and the identification of the person dispensing the drug.

All empty/used study drug packaging will be inventoried by the site and verified by the site monitor. Empty/used study drug packaging should be returned by the subject at each visit for accountability and compliance purposes and new packaging issued as necessary. Empty/used packaging will be retained (unless prohibited by local law) until the site monitor is on site to confirm the returned study drug. Site monitor(s) and site staff will complete study drug accountability via IRT, source documents, subject dosing diaries, and by visually inspecting the packaging whenever possible. After drug accountability has been completed, used packaging and unused study drug will be destroyed on site according to local procedures or regulations or returned to the destruction depot by the site monitor (for those sites that do not meet AbbVie's documentation requirements for on-site destruction). The use of a third party vendor for drug destruction must be pre-approved by AbbVie. For sites performing on-site drug destruction or using a third party vendor for drug destruction, a copy of the destruction methodology and date of destruction should be maintained at the site's facility.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

ABT-494 (upadacitinib) is a potent JAK1 selective inhibitor. The proposed study is a 88-week, randomized, double-blind, placebo-controlled study to compare multiple doses of ABT-494 versus placebo in moderate to severe AD adult patients that are candidates for systemic therapy. In order to assess the potential of ABT-494 to benefit patients with AD, patients with moderate to severe disease (baseline EASI \geq 16, BSA of \geq 10% and an IGA score \geq 3) will be enrolled and the mean percent change from Baseline in EASI score for different doses of ABT-494, compared to placebo will be assessed. The 16-week therapy (Period 1) is generally accepted as the timeframe during which an effective treatment would be expected to produce clinical benefit in AD. The 72-week double-

blind treatment period (Period 2) is to evaluate more long-term safety and efficacy of repeated administration of ABT-494 and to evaluate potential loss of response in AD subjects who have completed Period 1.

Placebo has been selected as the appropriate control group since, as discussed in Section 3.2, there is a lack of approved systemic therapies for moderate to severe AD, especially for long-term use.

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

This study will enroll adult female and male subjects who are at least of 18 years of age and are no more than 75 years of age at the time of the Screening visit; and have been diagnosed with moderate to severe AD. The study population selected in this study reflects the standard population for AD trials with new interventions.

5.6.4 Selection of Doses in the Study

This study is designed to evaluate the safety and efficacy and to define the dose- and exposure-response relationships of ABT-494 (upadacitinib) in subjects with moderate to severe AD. Doses in this study are selected based on efficacy and safety results from two Phase 2 studies in patients with rheumatoid arthritis (RA). In the Phase 2 studies in RA, all the evaluated doses of ABT-494 immediate release capsule formulation (3 mg BID, 6 mg BID, 12 mg BID, 18 mg BID, and 24 mg QD) were generally well-tolerated and without unexpected safety signals. The Phase 2 dose-response and exposure response results in RA show that the 6 mg BID dose of the immediate release formulation

approaches the plateau of efficacy in RA, and increasing the dose to 12 mg BID appears to result in some incremental efficacy benefit.

In order to enhance patients' compliance and to provide a more convenient dosing regimen than BID administration, AbbVie developed a once-daily tablet formulation which will be used in the current study.

The 15 mg and 30 mg QD doses of the once-daily formulation used in this study achieve equivalent daily area under the plasma concentration-time curve, and comparable maximum and minimum plasma concentration during a day to the 6 mg BID and 12 mg BID immediate release doses, respectively. Evaluating the 7.5 mg QD dose aims to ensure that the minimally efficacious dose is characterized.

The maximum dose for this study will not exceed 30 mg per day for 88 weeks to limit potential drug-related toxicity.

6.0 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 after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For AEs, please refer to Section 6.1 through Section 6.1.1. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drug, and any action(s) taken. For serious AEs considered as having "no reasonable possibility" of

being associated with study drug, the investigator will provide an Other cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.7 regarding toxicity management) and/or if the investigator considers them to be AEs.

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

Expected manifestations of AD (i.e., itching, excoriations, oozing, crusting, erythema, etc.) should not be reported as AEs unless considered to be a worsening of the underlying disease.

6.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the SAE.

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.
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For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study (see detailed toxicity management in Section 6.1.7):

- Serious infections
- Opportunistic infections
- Malignancy
- Hepatic Disorder
- Gastrointestinal perforations
- Anemia
- Neutropenia
- Herpes Zoster
- Creatine Phosphokinase (CPK Elevation)
- Decreased lymphocyte counts
- Renal Dysfunction
- Tuberculosis

- Adjudicated cardiovascular events
- Cardiac Arrhythmias

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each AE:

When criteria are available, events should be graded as described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), which can be accessed at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc.

If no grading criteria are provided for the reported event, then the event should be graded as mild, moderate, or severe per the investigator's judgment.

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

6.1.3 Relationship to Study Drug

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

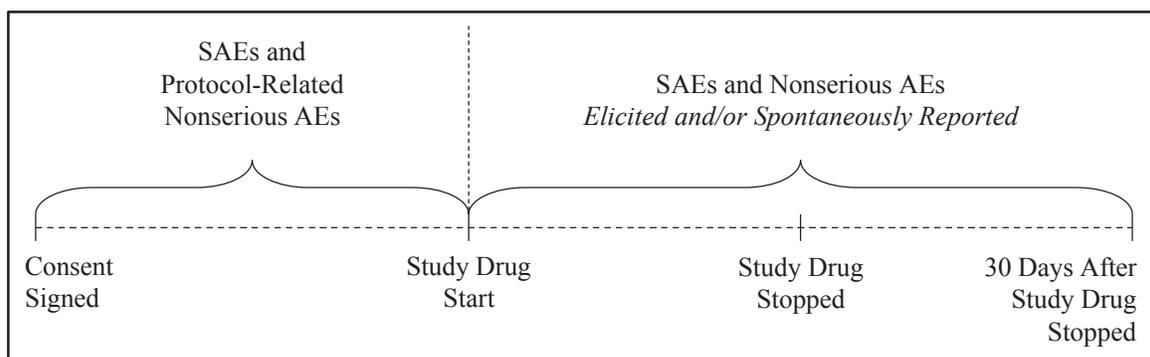
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All AEs reported from the time of study drug administration until 30 days, following discontinuation of study drug administration have elapsed, whether solicited or spontaneously reported by the subject. AEs will be collected from the time of study drug administration until completion of this study. In addition, SAEs and protocol-related non-SAEs will be collected from the time the subject signed the study-specific informed consent.

AE information will be collected as shown in [Figure 3](#).

Figure 3. Adverse Event Collection



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

In the case of any of the following reported events, an appropriate supplemental MACE eCRF should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures (SAE Supplemental Procedure eCRF).

In the case of certain AEs, the corresponding supplemental AE eCRF should be completed:

- Hepatic;
- Renal;
- Herpes Zoster Infection;
- CPK increases considered by the investigator to be an AE.

6.1.5 Serious Adverse Event

In the event of a SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) RAVE[®] system. SAE that occur prior to the site having access to the RAVE[®] system or if RAVE is not operable can be Emailed (this is the preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the SAE.

Email:	[REDACTED]
FAX to	[REDACTED]

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
[REDACTED]
1 North Waukegan Road
North Chicago, IL 60064

Phone: [REDACTED]
Email: [REDACTED]

For any subject safety concerns, please contact the AbbVie Therapeutic Area Scientific Director listed below; who will discuss with the AbbVie Medical Director as needed.



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

Phone: [REDACTED]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for ABT-494 (upadacitinib).

In Japan, the principal investigator will provide documentation of all SAEs to the Director of the investigative site and the Sponsor.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject or the partner of an enrolled subject and the outcome of the pregnancy will be collected. Pregnancies in study female subjects and female partners of male subjects will be collected from the date of the first dose through 30 days following the last dose of study drug.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Subjects and their partners should avoid pregnancy throughout the course of the study, starting with the Screening Visit through 30 days after the last study drug administration

for female subjects and through 30 days after the last study drug administration for male subjects. Male subjects should refrain from donating sperm for up to 30 days post last dose of study drug. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

6.1.7 Toxicity Management

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

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

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Re-challenge with study drug may occur once the infection has been successfully treated. If study drug has been interrupted for more than 14 consecutive days in Period 1 or more than 21 consecutive days in Period 2, the subject must be

discontinued from the study drug. Subjects who develop active TB must be discontinued from the study drug.

Serious Gastrointestinal Events: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued from the study drug.

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

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

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant OR a confirmed absolute QTcF value > 500 msec.

Management of Select Laboratory Abnormalities: For any given confirmed laboratory abnormality (confirmation by repeat testing with a new sample), 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 6](#) and may require an appropriate supplemental eCRF be completed.

Table 6. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	<ul style="list-style-type: none"> • If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with new sample • If hemoglobin decreases \geq 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 \geq 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	<ul style="list-style-type: none"> • If confirmed < 1000/μL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its baseline value. • Discontinue study drug if confirmed < 500/μL by repeat testing with new sample.
Absolute lymphocyte counts (ALC)	<ul style="list-style-type: none"> • If confirmed < 500/μL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its baseline value.
Total white blood cell count	<ul style="list-style-type: none"> • If confirmed < 2000/μL by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to normal reference range or its baseline value.
Platelet count	<ul style="list-style-type: none"> • If confirmed < 50,000/μL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

Table 6. Specific Toxicity Management Guidelines for Abnormal Laboratory Values (Continued)

Laboratory Parameter	Toxicity Management Guideline
AST or ALT	<ul style="list-style-type: none"> • Discontinue study drug if confirmed ALT or AST $> 3 \times$ ULN by repeat testing with new sample and either total bilirubin $> 2 \times$ ULN or international normalized ratio > 1.5 <ul style="list-style-type: none"> ○ INR will only be measured in subjects with ALT or AST $> 3 \times$ ULN by the central lab by reflex testing and confirmation is not needed for consideration in toxicity management criteria. • Discontinue study drug if confirmed ALT or AST $> 3 \times$ ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$). • Discontinue study drug if confirmed ALT or AST $> 8 \times$ ULN by repeat testing with new sample. • Discontinue study drug if confirmed ALT or AST $> 5 \times$ ULN by repeat testing with new sample for more than 2 weeks. <p>For all of the above ALT or AST elevation scenarios, complete supplemental hepatic eCRF.</p>
Serum Creatinine	<ul style="list-style-type: none"> • If serum creatinine is $> 1.5 \times$ the baseline value and $> \text{ULN}$, repeat the test for serum creatinine (with subject in an euvoletic state) to confirm the results. If the results of the repeat testing still meet this criterion then interrupt study drug and re-start study drug once serum creatinine returns to $\leq 1.5 \times$ baseline value and $> \text{ULN}$. • If confirmed serum creatinine $\geq 2.0 \text{ mg/dL}$, interrupt study drug and re-start study drug once serum creatinine returns to normal reference range or its baseline value. <p>For the above serum creatinine elevation scenarios, complete supplemental renal eCRF.</p>
Creatine Phosphokinase	<ul style="list-style-type: none"> • If any confirmed CPK value $\geq 4 \times \text{ULN}$ (if symptomatic or asymptomatic), complete supplemental CPK eCRF. • If confirmed CPK $\geq 4 \times \text{ULN}$ accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug, complete supplemental CPK eCRF, and contact the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director.

For allowed study drug interruption, the following rules apply:

- For ABT-494/placebo (daily dosing):

- Allow study drug interruption up to ≤ 14 consecutive days for AEs and emergency surgery during Period 1.
- In Period 2 (after Week 16), study drug interruption due to AEs/surgery is allowed ≤ 21 consecutive days.
- Elective surgery during Period 1 (up to Week 16) is not allowed. Elective surgery during Period 2 only up to the Week 40 visit is discouraged and needs to be discussed with the AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie Medical Director. If the subject undergoes elective surgery, the study drug should be interrupted 1 week prior to the planned surgery. 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.

6.1.8 Data Monitoring Committee

An external DMC will review unblinded safety data. See Section 5.5.5.1 for details.

6.1.9 Cardiovascular Adjudication Committee

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

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) 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 (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:

Alternate Contact:



Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

Examples of protocol deviations include the following:

- Subject entered into the study even though she/he did not satisfy entry criteria;
- Subject who developed withdrawal criteria during the study and was not withdrawn;
- Subject who received wrong treatment or incorrect dose;
- Subject who received excluded or prohibited concomitant treatment.

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the safety and efficacy of multiple doses of ABT-494 (upadacitinib) versus placebo, and assess the dose-response relationships among the three ABT-494 treatment groups and placebo group. Pairwise comparison of each ABT-494 treatment group versus placebo will be performed for all

primary and secondary endpoints in Period 1. Descriptive summaries will be provided for all treatment groups in Period 2.

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

8.1.1 Analysis Populations

The Intent-to-Treat (ITT) Subject Population, including all randomized subjects, will be used for the efficacy analyses. ITT populations will be defined for Period 1 and Period 2. The ITT Population in Period 1 is defined as all subjects who are randomized at Day 1. The ITT Population in Period 2 is defined as all subjects who are re-randomized at the entry of Period 2.

A Per-protocol Population will be defined if deemed necessary to exclude subjects with major protocol violations. The criteria for excluding subjects from the Per-protocol Population will be defined in the SAP and subjects to be excluded from the Per-protocol Population will be finalized before database lock and blind break. The Per-protocol Population, if defined, will be used to analyze the primary efficacy endpoint and key secondary efficacy endpoints.

The Safety Population, including all randomized subjects who receive at least one dose of study drug, will be used for the safety analysis. Safety populations will be defined for Period 1 and Period 2. The Safety Population in Period 1 is defined as all subjects who are randomized and receive at least one dose of study drug in Period 1. The Safety Population in Period 2 is defined as all subjects who are re-randomized at the entry of Period 2 and receive at least one dose of study drug in Period 2.

For efficacy analysis, subjects will be included in the treatment group to which they are randomized, regardless of which treatment the subjects actually received. The Safety will be analyzed by treatment group as treated.

8.1.2 Planned Methods of Statistical Analysis

Unless otherwise specified, all statistical tests will be two-sided significance level of 0.05. A test will be deemed significant if the *P* value rounded to three decimal places is less than or equal to 0.050 unless otherwise specified. Descriptive statistics will be provided including the number of observations, mean, median, standard deviation, minimum, and maximum for continuous variables, and counts and percentages for discrete variables.

8.1.3 Subject Accountability, Disposition and Study Drug Exposure

8.1.3.1 Subject Accountability

The following information will be summarized by site and by treatment group, as well as overall: number of subjects randomized, the number of subjects who received at least one dose of study drug, the number of subjects who completed the study, and the number of subjects who prematurely discontinued.

8.1.3.2 Subject Disposition

The number and percentage of subjects who are randomized, received at least one dose of study drug, prematurely discontinued, and completed the study will be summarized by treatment group and overall. Reasons for premature discontinuation of study drug will be summarized for all randomized subjects by treatment group and overall, with frequencies and percentages by reason for discontinuation.

8.1.3.3 Study Drug Exposure and Compliance

Exposure to study drug will be summarized for the Safety Populations in Period 1 and Period 2. The exposure to study drug (days) will be summarized with the mean, standard deviation, median, and range for each treatment group. The exposure to study drug is defined as the difference between the dates of the first and last doses of the study drug plus 1 day. Study drug compliance will also be summarized for each treatment group. The compliance is defined as the number of tablets taken (i.e., the difference between the number of tablets dispensed and the number of tablets returned) during the subject's

participation in the study divided by the number of tablets a subject is supposed to take each day times the length of time that the subject was in the Treatment Phase of the study.

8.1.4 Demographics and Baseline Characteristics

Demographics and Baseline characteristics of the study subjects will be summarized for each arm of the study using descriptive statistics.

Summary statistics for continuous variables will include the number of observations, mean, standard deviation, median, and range for each treatment group, and will be compared among treatment groups using analysis of variance (ANOVA). For other categorical or discrete variables, frequencies and percentages will be computed in each category for each treatment group, as well as for all subjects combined, and will be compared among treatment groups using chi-square test or Fisher's exact test (if 25% of the cells have expected counts less than 5).

8.1.5 Statistical Analyses of Efficacy

The efficacy analysis will be conducted in the ITT Population, and Per-protocol Population if defined, in each Period. Visit windows and the data handling conventions for summarizing efficacy results will be defined in the Statistical Analysis Plan. Missing data will be imputed using the following methods for the efficacy analyses in the ITT Populations:

- Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who has missing value at a specific visit as non-responder for that visit. In NRI analysis, subjects who prematurely discontinue study drug will be considered non-responders on or after discontinuation date. NRI will be the primary approach for binary endpoints.
- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit to impute missing data at later visits. Baseline value will not be carried forward. LOCF will be the primary approach in the analysis of continuous variable, and the secondary approach in the analysis of categorical variables.

- As-observed (OC): The OC analysis will not impute values for missing evaluations, and thus a subject who did not have an evaluation on a scheduled visit will be excluded from the as observed analysis for that visit. As-observed analysis will be the secondary approach in the analysis of continuous variables.
- Multiple Imputation (MI): The MI analysis imputes missing data multiple times under appropriate random variation and thus generates multiple imputed "pseudo-complete" datasets. Results will be aggregated across the multiple imputed datasets, overcoming drawbacks of the single imputation methods. MI will be performed for the primary efficacy variable and the proportion of subjects achieving IGA of "clear" or "almost clear" and EASI 75 at Week 16.

Efficacy parameters for the subjects who are rescued with 30 mg ABT-494 or topical corticosteroids in Period 2, and subjects who discontinued study drug due to EASI score worsening during Period 1 will be imputed from the point of rescue using non-responder imputation for categorical variables or LOCF for the continuous variables.

8.1.5.1 Primary Analysis of Efficacy

Primary efficacy endpoint is the percent change in EASI from baseline at Week 16. The comparisons between an ABT-494 (upadacitinib) treatment groups and placebo on primary efficacy endpoints will be performed using MCPMod approach.

The primary analysis will be carried out in the ITT Population and the Per-protocol Population, if defined.

LOCF will be used as primary approach for missing values. Sensitivity analyses using Multiple Imputation will be performed for the primary efficacy endpoint, EASI 75, and IGA 0 or 1.

Primary efficacy endpoint will also be analyzed using an appropriate model and terms included in the model for baseline characteristics. Due to likely small numbers, investigational site effects will not be fitted in the model.

The dose-response relationships among the three ABT-494 treatment groups and placebo group will be characterized for the primary endpoint at Week 16 using MCPMod approach. The following models will be considered: linear, E_{\max} , exponential, logistic and $\text{sig}E_{\max}$. The MCPMod approach for trial analysis stage consists of two main steps: MCP and Mod step. The MCP step focuses on establishing evidence for a drug effect across the doses, i.e., detecting a statistically significant dose response signal for the clinical endpoint and patient population investigated in the study. This step will typically be performed using an efficient test for trend, adjusting for the fact that multiple candidate dose response models are being considered. If a statistically significant dose response signal has been established, one proceeds with determining a reference set of significant dose response models by discarding the non-significant models from the initial candidate set.

The MCP step in MCPMod approach will typically be performed using an efficient test for trend, adjusting for the fact that multiple candidate dose response models are being considered.

The fitted curve for response function will be shown graphically with confidence intervals for each dose. Estimates of the treatment differences in response function and the associated 90% and 95% confidence intervals (CIs) for each active dose against placebo will be calculated from the model.

These results will be back-transformed to provide point estimates of the treatment difference in the primary efficacy endpoint and the associated 90% and 95% confidence intervals. The validity of the given dose-response model will be tested. Should any of the assumptions of the proposed analysis procedures not be met, alternative procedures will be implemented and fully documented.

8.1.5.2 Secondary Analysis of Efficacy

For binary endpoints, frequencies and percentages will be reported for each treatment group. Pairwise comparison of each ABT-494 group and placebo will be performed using the Cochran Mantel-Haenszel test adjusting for stratification factors.

For continuous endpoints, the mean, standard deviation, median, and range will be reported for each treatment group. Pairwise comparisons for each of the ABT-494 treatment groups and the placebo group will be carried out using the analysis of covariance (ANCOVA) model with treatment group as the fixed factor, and the corresponding baseline value and the stratification factors as the covariates.

Time to event variables will be analyzed by stratified log-rank test adjusting for stratification factors.

Proportion of subjects achieving EASI 75 at Week 16 and proportion of subjects achieving IGA of "clear" or "almost clear" at Week 16 will also be analyzed by demographic subgroups including age, gender, weight, body mass index, race and geographical region. Additional subgroup analysis based on baseline characteristics may be conducted.

8.1.6 Safety Analysis

8.1.6.1 General Considerations

Safety analyses will be carried out using the Safety Population, in each period, and is based on treatments actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, ECG, and vital signs. Frequency tables and lists of subjects with treatment-emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from baseline to defined time points will be tabulated.

Missing safety data will not be imputed.

8.1.6.2 Analysis of Adverse Events

8.1.6.2.1 Treatment-Emergent Adverse Events (TEAE)

AEs will be coded using MedDRA. A TEAE is defined as an AE that began or worsened in severity after initiation of study drug.

AEs starting more than 30 days following the last dose of study drug will not be included in summaries of TEAEs.

As a general safety summary, the number and percentage of subjects experiencing TEAEs will be summarized for each treatment group for the following AE categories:

- All AEs;
- All severe AEs;
- All reasonably possibly related AEs;
- All SAEs;
- Frequent AEs (reported in 5% of subjects or more in any treatment group);
- Frequent reasonably possibly related AEs (reported in 5% of subjects or more in any treatment group);
- Discontinuations due to AEs;
- Death.

TEAEs will also be summarized separately for the period when subjects receive ABT-494 monotherapy, the period when subjects receive concomitant mometasone furoate, and the period when subjects receive concomitant triamcinolone acetonide.

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

TEAEs will be summarized and presented by system organ classes (SOCs) and preferred terms (PTs) using MedDRA. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

TEAE will also be summarized by maximum severity and by maximum relationship.

- The AEs of special interest (including but not limited to serious infections, opportunistic infections, malignancy, hepatic disorder, gastrointestinal perforations, anemia, neutropenia, herpes zoster, creatine phosphokinase (CPK elevation), decreased lymphocyte counts, renal dysfunction, tuberculosis, adjudicated cardiovascular events, cardiac arrhythmias) will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the combined safety analysis of Period 1 and Period 2.

All AEs leading to discontinuation will be presented in listing format. A listing by treatment group of TEAEs grouped by SOC and MedDRA preferred term with subject identification numbers will be generated.

8.1.6.2 Serious Adverse Events and Death

All treatment-emergent SAEs and AEs leading to death will also be presented in listing format. In addition, SAEs will be summarized by SOC and MedDRA PT.

8.1.6.3 Analysis of Laboratory, Vital Sign, and ECG Data

Changes from baseline by visit, and changes from baseline to minimum value, maximum value, and final values in continuous laboratory data, and vital signs will be summarized by treatment group.

The laboratory data will be categorized as low, normal, or high based on the normal ranges of the laboratory used in this study. The shift tables will tabulate the number and percentage of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range. Shift tables for

liver elevations from baseline to post baseline maximum value will be summarized for each treatment group.

Listings will be provided for potentially clinically significant laboratory values and vital signs.

Analysis details will be specified in the SAP.

8.1.7 Interim Analysis

The analysis of the double-blind 16-week period of the study (Period 1), including the primary endpoint analysis, will be conducted after all subjects have either completed the Period 1 or discontinued from the study; and the data regarding Period 1 have been cleaned and an interim database lock is performed. This efficacy analysis is the only and final analysis of the double-blind Period 1, thus no adjustment of alpha-level is needed. In addition, there will be an interim analysis after all subjects have either reached Week 32 or discontinued from the study; and the data is cleaned.

8.1.8 Pharmacokinetic and Exposure-Response Analyses

Individual ABT-494 (upadacitinib) plasma concentrations at each study visit will be tabulated and summarized with appropriate statistical methods.

Data from this study may be combined with data from other studies for the population pharmacokinetic and exposure-response analyses. Population pharmacokinetic and exposure-response analyses of only data from this study may not be conducted. The following general methodology will be used for the population pharmacokinetic and exposure-response analyses.

Population PK analyses will be performed using the actual sampling time relative to dosing. PK models will be built using a non-linear mixed-effects modeling approach with NONMEM software (Version 7, or a higher version). The structure of the starting PK model will be based on the PK analysis of data from previous studies. The CL/F and V/F of ABT-494 will be the PK parameters of major interest in the analyses. If necessary,

other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis.

The evaluation criteria described below will be used to examine the performance of different models.

1. The objective function of the best model is significantly smaller than the alternative model(s).
2. The observed and predicted concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the alternative model(s).
3. Visual inspection of model fits, standard errors of model parameters and change in inter-subject and intra-subject error.

Once an appropriate base PK model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, body weight, concomitant medications, laboratory markers of hepatic or renal function, etc.) will be explored using stepwise forward selection method, or another suitable regression/smoothing method at a significance level of 0.05. After identification of all relevant covariates, a stepwise backward elimination of covariates from the full model will be employed to evaluate the significance (at $P < 0.005$, corresponding to a decrease in objective function > 7.88 for one degree of freedom) of each covariate in the full model.

Linear or non-linear relationships of primary PK parameters with various covariates will be explored.

Relationships between ABT-494 exposure and clinical observations (primary efficacy variable) will be explored. Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored. The relationship between exposure (e.g., population PK model predicted average concentrations, area under the curve, trough concentrations, the individual model-predicted PK profiles, or some other appropriate measure of exposure) and drug effect will be explored. Several classes of models (e.g., linear, log-linear, exponential, E_{max} , sigmoid E_{max} , etc.) will be evaluated to characterize the exposure-response relationship based on observed data. Results of the PK and exposure-response analyses may be summarized in a separate report prior to regulatory filing of ABT-494 (upadacitinib) for the treatment of RA, rather than in the CSR.

Additional analyses will be performed if useful and appropriate.

8.1.9 Statistical Analysis of Biomarker Data

Summary statistics for the in vivo pharmacodynamic biomarkers (NK, NKT, B cells, and T cells) at baseline and post-treatment time points (Weeks 8 and 16 or PD), in addition to change from baseline at each time will be provided; this will include mean, standard deviation, median, quartiles, and range for each group. The pharmacodynamic effect of each biomarker between the placebo and ABT-494 (upadacitinib) treatment groups will be evaluated via a non-linear mixed-effects modeling approach with Change from baseline of the biomarker as response variable, Treatment, Time, and Treatment \times Time interaction as fixed-effects, the corresponding baseline biomarker score as a covariate, and "subjects nested within the treatment group" as a random-effect. Other baseline variables such as age, weight, etc., may be considered as appropriate. For biomarkers identified to have significant overall treatment effect via the non-linear mixed-effects modeling analysis, dose-response models with the biomarker as a continuous response will be explored. In addition to the above analyses of biomarkers individually, the effect of certain combination of biomarkers on the treatment groups may be explored. If the optional exploratory research/validation studies variables, including an additional panel of prognostic, predictive, surrogate and pharmacodynamic biomarkers are evaluated, then

those data may be analyzed as follows. The association of biomarkers to the efficacy and safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling algorithms. Optimal multivariate combinations of biomarkers that associate with efficacy endpoints, subject response/non-response (with respect to appropriate clinical endpoints), and also with safety endpoints may be explored via a variety of statistical predictive modeling algorithms. Also cut-points for individual biomarkers and optimal combinations of biomarkers that differentiate the subject response with respect to efficacy/safety endpoints may be explored. The significance of these multivariate combinations of biomarkers may be assessed via at least 20 iterations of 5-fold cross-validation.

Analyses will be performed for each of IL-6 induced STAT3 phosphorylation, IL-7-induced STAT5 phosphorylation and GMCSF induced STAT5 phosphorylation as measured in a whole blood ex vivo assay. Descriptive statistics will be provided by dose level (with placebo considered a dose level) for the measure of phosphorylation at each scheduled time point of evaluation. Descriptive statistics will also be provided for the percent inhibition of phosphorylation for each of the post dose times of evaluation, with the pre-dose measurement from the first day of the ABT-494 regimen as the baseline value. For each day of serial measurements, a repeated measures analysis will be performed on the measure of phosphorylation. Alternatively, the analysis may be performed on the percent inhibition of phosphorylation. In either case the baseline measurement of phosphorylation will be a covariate. If the responses have a probability distribution that is meaningfully non-symmetric, a transformation will be sought to produce an approximately symmetric distribution. Also, if percent inhibition is analyzed and if the variances for the various dose levels appear to differ so that incorrect conclusions may be reached, a transformation may be employed to achieve more nearly equal variances.

8.2 Determination of Sample Size

Approximately 160 subjects will be randomized to three treatment groups and placebo in a ratio of 1:1:1:1. The sample size for this study is based on the percent change in EASI

from baseline at Week 16. Assuming a percent change in EASI from baseline at Week 16 of 35, 45, 60, and 70 in the placebo, 7.5 mg, 15 mg, and 30 mg arms with a standard deviation 40 and a maximum efficacy of 80, a sample size of 40 subjects per treatment group is sufficient to test for the presence of a dose response signal, to select the best dose response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest (e.g., the minimum effective dose, MED) using MCP-Mod (Multiple comparison procedure and modeling) approach. This approach provides 99% average power to detect a dose effect at 5% level of significance (one-sided) with the linear, E_{\max} , exponential, logistic and $\text{sig}E_{\max}$ models pre-specified as likely candidates to characterize the dose-response for ABT-494 for the percent change in EASI.

A sample of size 40 per group provides 97% power to detect a significant difference between 30 mg QD and placebo, and 78% power to detect a significant difference between 15 mg QD and placebo at two-sided level of significance of 5.0%.

8.3 Randomization Methods

Subjects will be randomly assigned in a 1:1:1:1 ratio to one of the four treatment groups per the study design diagram [Figure 1](#) in Period 1. Randomization will be stratified by geographic region (US/PR/Canada, EU/AUS, and Japan).

Subjects who complete Period 1 will be randomized at Week 16 to the 72-week double-blind treatment period (Period 2) in a 1:1 ratio within the treatment group in Period 1. Randomization will be stratified by geographic region (US/PR/Canada, EU/AUS, and Japan) and EASI 75 response at Week 16.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and

any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (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 clinical investigator are specified in [Appendix A](#).

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in

the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

The skin biopsies and samples for exploratory research/validation studies will only be collected if the subject has voluntarily signed and dated the separate written consents for skin biopsies and exploratory research/validation studies, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consents must be signed before the skin biopsies and exploratory research/validation studies samples are collected and testing is performed. If the subject does not consent to the exploratory skin biopsies and research/validation studies, it will not impact the subject's participation in the study.

Selected sites will be asked to perform a complete investigation of biomarkers. For such sites, these assessments (blood sample and skin biopsy collections) will be made mandatory as part of the main study. There will be a specific ICF for subjects in these selected sites.

In the event a subject withdraws from the main study, optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the

subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic

media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave[®] provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Electronic Patient Reported Data:

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

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

The ePRO data of DLQI, MOS-R, POEM, PGIS, Asthma Symptoms, and Daytime Nasal Symptoms Questionnaires will be collected electronically via an onsite tablet device into which the patient will directly enter the required pieces of information at visits specified in [Table 2](#). The electronic tablet device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for patients to complete more than one of the same assessments at any one visit. The daily pruritus NRS, [REDACTED] ADerm-SS, and [REDACTED] ADerm-IS ePROs will be collected from patients electronically every evening via a handheld device provided to the subject at Screening. Hand-held device usage stops at the Week 40 visit. The handheld electronic device will be programmed to allow data entry once per day. All data entered on the devices will be immediately stored to the devices itself and automatically uploaded to a central server

administrated by CRF Health. The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

Electronic Actigraphy Data:

Patient data on sleep activity and scratching events must be collected for each subject screened/enrolled in this study. Some of these data are being collected with an electronic actigraphy wearable watch device called Geneactiv Scratching Device, provided by the technology vendor Philips of Andover, MA, USA. The actigraphy system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the actigraphy system is available through the vendor, Philips.

All data collected on the devices will be manually uploaded by site staff during the study visits outlined in [Table 2](#) to a central server administrated by Philips. The data on the server will be considered source; and maintained and managed by Philips.

Detailed instructions for the actigraphy devices and data uploading will be provided in the Philips custom instruction manual for this study.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

All information concerning ABT-494 (upadacitinib) and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of ABT-494. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any research/validation studies that may be using optional and mandatory exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to

subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional and mandatory exploratory research/validation studies from this study may be provided to investigators and used in scientific publications or presented at medical conventions. Optional and mandatory exploratory research/validation studies data will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

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

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for ABT-494 (upadacitinib).
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study to Evaluate ABT-494 (Upadacitinib) in Adult Subjects with Moderate to Severe Atopic Dermatitis

Protocol Date: 30 August 2017

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
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., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
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 investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
		Clinical Development, Immunology
		Clinical Development, Immunology
		Clinical Development, Immunology
		Pharmacovigilance and Patient Safety
		Data and Statistical Sciences
		Clinical Pharmacokinetics
		Clinical Operations

Appendix C. TB Risk Assessment Form Example

1. Have you or an immediate family member or other close contact ever been diagnosed or treated for tuberculosis?
2. Have you lived in or had prolonged travels to countries in the following regions:
 - Africa
 - Eastern Europe
 - Asia
 - Latin America
 - Caribbean Islands
 - Russia
3. Have you lived or worked in a prison, homeless shelter/refugee camp, immigration center, health care worker in a hospital or nursing home?
4. Have you, or an immediate family member, had any of the following problems for the past 3 weeks or longer:
 - Chronic Cough
 - Chest pain, or pain with breathing or coughing
 - Blood-Streaked Sputum (coughing up blood)
 - Unexplained Weight Loss
 - Fever
 - Fatigue/Tiredness
 - Night Sweats
 - Shortness of Breath

From: <http://www.mayoclinic.org/diseases-conditions/tuberculosis/symptoms-causes/dxc-20188557>
http://www.in.gov/fssa/files/Tuberculosis_Questionnaire.pdf

Appendix D. Investigator's Global Assessment Example

Score	Short Description	Detailed Description
0	Clear	No inflammatory signs of atopic dermatitis
1	Almost Clear	Just perceptible erythema and just perceptible papulation/infiltration
2	Mild	Mild erythema and mild papulation/infiltration
3	Moderate	Moderate erythema and moderate papulation/infiltration
4	Severe	Severe erythema and severe papulation/infiltration with or without oozing/crusting

Appendix E. Eczema Area and Severity Index (EASI) Scoring Example

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

Assignments for the following body regions are as follows:

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

Area Score

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

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

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

Severity Score

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

The four signs are:

1. Redness (erythema, inflammation)
2. Thickness (induration, papulation, swelling – acute eczema)
3. Scratching (excoriation)
4. Lichenification (lined skin, prurigo nodules – chronic eczema)

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

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

0 = None, absent

1 = Mild

2 = Moderate

3 = Severe

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

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

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

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

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

Appendix F. SCORing Atopic Dermatitis (SCORAD) Example

The SCORAD is a tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD.²⁰

Body Area Affected:

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

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

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

Symptom Severity:

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

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

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

Subjective Symptoms:

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

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

PRURITUS (0to10)	<input type="text"/>	0	10
SLEEP LOSS (0to10)	<input type="text"/>		

(10 cm in length)

SCORAD Calculation:

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

Appendix G. Dermatology Life Quality Index (DLQI) Example

DERMATOLOGY LIFE QUALITY INDEX

Hospital No:	Date:	Score:	DLQI
Name:	Diagnosis:		<input type="text"/>
Address:			

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

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

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

Please check you have answered EVERY question. Thank you.

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Appendix H. Pruritus (Itch) Numerical Rating Scale (NRS) Example

Pruritus/Itch Numeric Rating Scale



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Appendix I. Medical Outcomes Study (MOS) Sleep Scale-Revised Example

Your Sleep

For each of the following questions, please mark an in the one box that best describes your answer.

1. How long did it usually take for you to fall asleep during the past 4 weeks?

0-15 minutes	16-30 minutes	31-45 minutes	46-60 minutes	More than 60 minutes
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number of hours per night:

3. How often during the past 4 weeks did you...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a	feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b	get enough sleep to feel rested upon waking in the morning?				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c	awaken short of breath or with a headache?				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d	feel drowsy or sleepy during the day?				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e	have trouble falling asleep?				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

How often during the past 4 weeks did you...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
f	awaken during your sleep time and have trouble falling asleep again?.....				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g	have trouble staying awake during the day?.....				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h	snore during your sleep?.....				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i	take naps (5 minutes or longer) during the day?.....				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
j	get the amount of sleep you needed?.....				
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Copyright, 1986, RAND.
MOS 12-Item Sleep Scale – Revised 2010
United States (English)

Appendix J. Patient Oriented Eczema Measure (POEM) Example



POEM for self-completion

Patient Details: _____

Date: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

POEM for self-completion

How is the scoring done?

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

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

Note:

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

What does a poem score mean?

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

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

Do I need permission to use the scale?

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

References

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

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Appendix K. Asthma Symptoms Questionnaire Example



Appendix L. Daytime Nasal Symptoms Questionnaire Example



Appendix M. Atopic Dermatitis Symptom Scale (ADerm-SS) Questionnaire Example







**Appendix N. Atopic Dermatitis Impact Scale (ADerm-IS) Questionnaire
Example**





Appendix O. Patient Global Impression of Severity (PGIS) Questionnaire Example



Appendix P. Local Canada Requirements

Section 5.2.1, Inclusion Criteria

10. If female of childbearing potential, must be practicing at least two reliable methods of contraception (one highly effective method combined with one effective method, refer to Section 5.2.4), that are effective from Study Day 1 through at least 30 days after the last dose of study drug.
11. If male, and subject is sexually active with the female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of study drug, to practice the protocol-specified contraception (refer to Section 5.2.4).

Section 5.2.4, Contraception Recommendations

Contraception Recommendation for Females

A woman who is postmenopausal or permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) is not considered to be a woman of childbearing potential and is not required to follow contraception recommendations.

Postmenopausal is defined as:

- Age \geq 55 years with no menses for 12 or more months without an alternative medical cause; or
- Age $<$ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level $>$ 40 mIU/L.

A woman who does not meet the definition of postmenopausal or permanently surgically sterile is considered of childbearing potential and is required to use two forms of contraception. This includes one form of highly effective contraception and one effective method of contraception. That is effective from Study Day 1 (or earlier) through at least 30 days after the last dose of oral study drug.

- Highly effective methods:
 - Hormonal contraceptives started at least 2 months prior to randomization (e.g., combined [estrogen and progestogen containing] [oral contraceptives, patch, vaginal ring, injectables, and implants]);
 - Intrauterine device (IUD) or intrauterine system (IUS);
 - Vasectomy and tubal ligation.
- Effective methods:
 - Barrier methods of contraception (e.g., male condom, female condom, cervical cap, diaphragm, contraceptive sponge)
 - Note: The proper use of diaphragm or cervical cap includes use of spermicide and is considered one barrier method. The cervical cap and contraceptive sponge are less effective in parous women. The use of spermicide alone is not considered a suitable barrier method for contraception. When used consistently and correctly, "double barrier" methods of contraception (e.g., male condom with diaphragm, male condom with cervical cap) can be used as an effective alternative to the highly effective contraception methods described above. Male and female condoms should not be used together as they can tear or become damaged.

Contraception Recommendation for Males

For a male subject who has a female partner who is postmenopausal or permanently sterile, no contraception is required.

A male subject who is sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 30 days after the last dose of oral study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the highly effective contraceptive methods (as defined in the protocol for female study subjects of childbearing potential).

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 30 days after the last dose of oral study drug.

Male subjects are responsible for informing his partner(s) of the risk of becoming pregnant and for reporting any pregnancy to the study doctor. If a pregnancy occurs, a partner authorization form requesting pregnancy outcome information will be requested from the pregnant partner.

Appendix Q. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 6.1.1.3 Adverse Events of Special Interest

Add: new tenth bullet

Decreased lymphocyte counts

Section 8.1.6.2.1 Treatment-Emergent Adverse Events (TEAE)

Eighth paragraph previously read:

The AEs of special interest (including but not limited to serious infections, opportunistic infections, malignancy, hepatic disorder, gastrointestinal perforations, anemia, neutropenia, herpes zoster, creatine phosphokinase (CPK elevation), renal dysfunction, tuberculosis, adjudicated cardiovascular events, cardiac arrhythmias) will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the combined safety analysis of Period 1 and Period 2.

Has been changed to read:

- The AEs of special interest (including but not limited to serious infections, opportunistic infections, malignancy, hepatic disorder, gastrointestinal perforations, anemia, neutropenia, herpes zoster, creatine phosphokinase (CPK elevation), decreased lymphocyte counts, renal dysfunction, tuberculosis, adjudicated cardiovascular events, cardiac arrhythmias) will be summarized. Event rate (per 100 patient years) for AEs of special interest will also be summarized for the combined safety analysis of Period 1 and Period 2.